FDA Executive Summary

Cartiva Synthetic Cartilage Implant

Prepared for the
April 20, 2016, Meeting of the
Orthopaedic and Rehabilitation Devices Panel of the Medical Devices Advisory Committee

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1. INTRODUCTION

The subject of this Executive Summary is the Cartiva Synthetic Cartilage Implant (or "Cartiva Implant") premarket approval (PMA) application, P150017, sponsored by Cartiva, Inc. The Cartiva Implant is made of an organic polymer-based biomaterial comprised of polyvinyl alcohol and saline. The device is designed to exude and reabsorb saline upon application and removal of a compressive load, in a manner similar to biologic cartilage. The viscoelastic implant material properties are intended to be conducive to replacing focal areas of painful damaged cartilage and are intended to allow for pain reduction and maintained range of motion. The finished device is a molded cylindrical implant that is placed into the metatarsal head in the first metatarsophalangeal (MTP) joint via press fit implantation. The implant has 2 sizes, 8mm (8 mm diameter x 8 mm depth) and 10 mm (10 mm diameter x 10 mm depth). The device is designed to penetrate the subchondral bone. This PMA application has been reviewed by staff in the Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) (also referred to as the Agency). Your time and effort in the review of this PMA application is greatly appreciated.

1.1 Rationale for Presentation to the Panel

In addition to the fact that the Cartiva Implant is a first-of-a-kind press fit, osteochondral plug that attempts to preserve motion of the first metatarsophalangeal joint for the proposed target population, the Agency is presenting this PMA application to the Orthopaedic and Rehabilitation Devices Panel of the Medical Devices Advisory Committee based on the reasons listed below. The study supporting this PMA application was conducted outside of the United States (oUS). Although this oUS study was not subject to prior approval under an Investigational Device Exemptions (IDE) application, extensive protocol feedback was nonetheless provided to the sponsor prior to the initiation of the study. The study was a non-inferiority comparison of subjects treated with the Cartiva Implant (or "Cartiva") and a control cohort of subjects undergoing an arthrodesis procedure (or "Arthrodesis"). In its review of the PMA, the Agency has raised concerns related to the study design, secondary surgical interventions, and study observations/results. Specifically, the Agency has identified issues related to the time of the study endpoint, differences in success criteria for each group, chosen non-inferiority margin, and criteria for determination of radiographic success or failure. The following cited issues impact the ability to analyze and interpret the study results for the purpose of assessing safety, effectiveness, as well as the benefits and risks of the Cartiva investigational device:

- The appropriateness of the chosen non-inferiority margin, 15%.
- Cartiva patients experiencing lower pain reduction from baseline at later time points as compared to Arthrodesis patients.
- The risk of secondary subsequent surgical interventions in Cartiva versus Arthrodesis.
- Assessment criteria for function and the respective function measures in Cartiva versus Arthrodesis.

- Assessment criteria for radiographic success and the respective radiographic success measures in Cartiva versus Arthrodesis.

- The Panel will be asked to comment on the need for, and elements of, a new enrollment for the Post-Approval Study, should FDA determine that this PMA application is approvable.

- The Panel will be asked a voting question on whether there is a reasonable assurance of safety for the PMA device for its proposed intended use.

- The Panel will be asked a voting question on whether there is a reasonable assurance of effectiveness for the PMA device for it proposed intended use.

- The Panel will be asked a voting question on whether a favorable benefit-risk has been demonstrated for the PMA device for its proposed intended use.

1.2 FDA Questions for the Panel

The FDA would like the Panel to provide responses to a series of questions regarding the safety and effectiveness data presented in the PMA application. These questions are located in the "FDA Panel Questions" section of the Panel package, and Panel input will be solicited at the April 20, 2016, Panel meeting.

2. DEVICE DESCRIPTION

2.1 Applicant Name and Address

CARTIVA, INC
6120 WINDWARD PARKWAY SUITE 200
ALPHARETTA, GA 30005 US

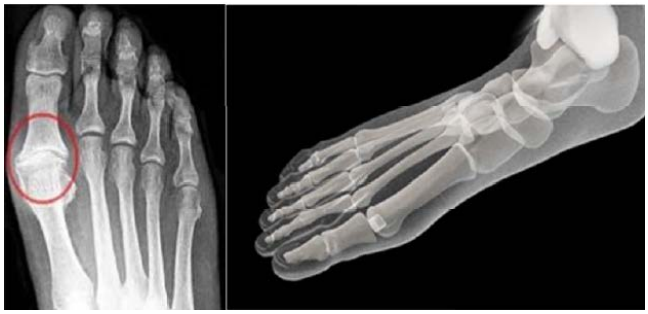
2.2 Description of the Cartiva Investigational Device

The Cartiva implant is made of an organic polymer-based biomaterial comprised of polyvinyl alcohol and saline. The device is designed to exude and reabsorb saline upon application and removal of a compressive load, in a manner similar to biologic cartilage. The viscoelastic implant material properties are intended to be conducive to replacing focal areas of painful damaged cartilage and are intended to allow for pain reduction and maintained range of motion. The finished device is a molded cylindrical implant that is placed into the metatarsal head in the first metatarsophalangeal (MTP) joint via press fit implantation.
The sponsor is proposing 2 sizes of their device 8mm (8 mm diameter x 8 mm depth) and 10 mm (10 mm diameter x 10 mm depth). The device is designed to penetrate the subchondral bone. At these sizes, the sponsor notes that the implant is expected to cover 37-49% of the 1st MTP joint surface (based on

geometrical dimensions of the 1st MTP joint measured by Yoshioka in the Journal of Orthopaedic Research[1].

Figure 1: Cartiva Synthetic Cartilage Implant

Figure 2: Implant Location of Cartiva Device



Instrumentation (Placer, Introducer, Metatarsal Drill Bit, and Sterilization Tray): The Cartiva instrumentation includes dedicated tools that accomplish drilling of an appropriately sized cavity in the intended target (the metatarsal head), and deploying the Cartiva device into the cavity via a press fit configuration. The Cartiva instrumentation, including the Placer, Introducer, Metatarsal Drill Bit, and Sterilization Tray are contract manufactured by approved suppliers. The guide pins (off-the-shelf Steinmann pins manufactured by Micro-aire Surgical Instruments) that have been qualified for use with the Cartiva instrumentation are received as final product direct from the manufacturer and will be distributed for use with the Cartiva instrumentation. Each piece of instrumentation is made of surgical grade stainless steel and is provided to the user non-sterile. All instrumentation outside of the guide pins are reusable and are provided with cleaning and sterilization instructions. The guide pins are provided with sterilization instructions and are disposed of after a single use. The device is stored in saline until use.

3. PROPOSED INDICATIONS, CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS

3.1 Indications for Use

The following Indications for Use are proposed by the sponsor in the PMA application:

"The Cartiva® Synthetic Cartilage Implant is intended for use in the treatment of patients with degenerative or post-traumatic arthritis in the first metatarsophalangeal joint in the presence of good bone stock along with the following clinical conditions: hallux valgus or hallux limitus, hallux rigidus, and an unstable or painful metatarsophalangeal joint."

3.2 Contraindications

The sponsor proposes that the use of the Cartiva Implant be contraindicated in the following cases:

- Active infection of the foot
- Known allergy to polyvinyl alcohol

[1] Yoshioka et al: Geometry of the first metatarsophalangeal joint. J Ortho Res: Volume 6, Issue 6, pages 878–885, November 1988

- Inadequate bone stock
- Diagnosis of gout with Tophi
- Any significant bone loss, avascular necrosis, and/or large osteochondral cyst (> 1cm) of the first metatarsophalangeal joint
- Lesions of the first metatarsal head greater than 10 mm in size
- Physical conditions that would tend to eliminate adequate implant support (e.g., insufficient quality or quantity of bone resulting from cancer, congenital dislocation, or osteoporosis), systemic and metabolic disorders leading to progressive deterioration of bone (e.g., cortisone therapies or immunosuppressive therapies), and/or tumors and/or cysts >1cm of the supporting bone structures

3.3 Warnings

The sponsor proposes that the following warnings be included in the labeling for Cartiva Implant:

- The safety and effectiveness of this device has not been established in subjects with the following conditions:
  - Skeletally immature subjects, pediatric or adolescent (< 21 years old)
  - Subjects on chronic anticoagulation due to a bleeding disorder or has taken
  - anticoagulants within 10 days prior to surgery
  - Subjects with osteonecrosis of the first metatarsophalangeal joint
  - Grade 0 or 1 osteoarthritis

3.4 Precautions

The sponsor proposes that the following precautions be included in the labeling for the Cartiva Implant:

- The Cartiva® SCI should only be used by surgeons who are experienced with orthopaedic procedures of the foot and have undergone training in the use of this device. Only surgeons who are familiar with the implant, instruments, procedure, clinical applications, biomechanics, adverse events, and risks associated with the Cartiva® SCI should use this device. A lack of adequate experience and/or training may lead to a higher incidence of adverse events.
- Preoperative planning should be performed by the surgeon to estimate the required implant size. Prior to surgery, assure that the appropriate implant sizes are available for surgery.
- Examine all instruments prior to surgery for wear or damage. Replace any worn or damaged instruments.
- Use aseptic technique when removing the Cartiva® SCI device from the innermost packaging.
- Carefully inspect the device and its packaging for any signs of damage, including damage to the sterile barrier. Do not use Cartiva® SCI implants if the packaging is damaged or the implant shows signs of damage.
- Use care when handling the Cartiva® device to ensure that it does not come in contact with objects that could damage the implant. Damaged implants are no longer functionally reliable.
- The Cartiva® SCI should not be used with components or instruments from other manufacturers.

- Surgical implants must never be re-used or re-implanted. Ensure proper alignment and placement of device components as misalignment may cause excessive wear and/or early failure of the device.

4. DEVICE HISTORY

4.1 Regulatory History

The safety and effectiveness of the Cartiva Synthetic Cartilage Implant was evaluated under a clinical study entitled, "A Prospective, Randomized, Non-Inferiority Study to Evaluate the Safety and Effectiveness of Cartiva Synthetic Cartilage Implant in the Treatment of First Metatarsophalangeal Joint Osteoarthritis as Compared to a Control" (or the MOTION study). Subjects were treated between October, 2009 and February, 2013. While the study was conducted in the United Kingdom and Canada and therefore was not subject to IDE regulations, extensive feedback had nonetheless been provided to the sponsor prior to initiation of the study. While some of the clinical study design issues raised by the Agency in its feedback were ultimately incorporated into the study protocol and adequately addressed by the sponsor at the time of PMA submission, others were not and are identified in this Summary.

4.2 Marketing History

The Cartiva device has been distributed since 2002 with approvals in Europe, Canada and Brazil. The sponsor states that over 4000 Cartiva implants have been distributed throughout the world to date. The device was originally manufactured and distributed by SaluMedica, Inc.; the proprietary technology and manufacturing processes were acquired by Carticept Medical in August 2008. The product line has since become a separate business entity, Cartiva, Inc., as of 2012. The device has not been withdrawn from any of the oUS markets.

5. BACKGROUND

The sponsor conducted the oUS study to treat patients with pain at the first MTP joint as a result of Osteoarthritis (OA). OA is the most widespread type of arthritis or joint disease, and is among the most frequent reported symptomatic health problems for middle aged and senior adults.[2,3] It is characterized by pain and dysfunction in the joint that is caused by degeneration, which includes progressive loss of articular cartilage, remodeling of the subchondral bone, and osteophyte formation. The incidence of OA in each of the human joints escalates with age, and may affect any of the synovial joints, though is most commonly found in the hand, foot, knee, spine, and hip joints.[1] The pathology of OA encompasses the entire joint and includes focal defects with continuing hyaline articular cartilage loss, concomitant changes to the subchondral bone, as well as marginal outgrowths, osteophytes, and increased thickening.

[2] Buckwalter JA, Saltzman C, Brown T. The Impact of Osteoarthritis. Clinical Orthopaedics and Related Research. 2004;427S:S6-S15.

[3] Lawrence RC, Felson DT, Helmick CG, Arnold LM, Choi H, Deyo RA, et al. Estimated of Prevalence of Arthritis and Other Rheumatic Conditions in the United States Part II. Arthritis and Rheumatism. 2008 January;58(1):26-35.

The first MTP joint, or hallux, is a modified hinge joint consisting of the metatarsal head and the proximal phalanx, which is intrinsically unstable, though it gains stability from an array of soft tissue structures that provide support.[4] The most frequent site of OA in the forefoot is in the first MTP joint. An array of disorders due to acquired orthopaedic abnormalities and traumatic injuries may contribute to the development of OA in the first MTP joint. These include primary OA or OA development due to trauma, repetitive microtrauma, rheumatoid arthritis, other inflammatory conditions, severe bunion deformities (hallux valgus), and recurrent hallux deformity after surgery.[5,6]

First MTP joint OA often presents with pain and limited range of motion due to the development of osteophytes on the dorsal aspect of the metatarsal head and the proximal phalanx.[7,8] Patients complain of pain with push off and an inability to wear shoes, which can force the hallux into dorsiflexion.[6] Hallux rigidus is a term typically used to depict the symptoms associated with degenerative arthritis of the first MTP joint.[9] It is characterized by a limitation in range of motion, which can progress from a functional limitation of motion, to differing degrees of degenerative OA.[5,10] The severity of degenerative changes is strikingly dependent upon the duration of symptoms.[11]

Hallux valgus is a static subluxation of the first MTP joint that has a lateral divergence of the hallux and medial divergence of the first metatarsal, and are often called bunions.[12] Per the American Academy of Orthopaedic Surgeons (AAOS), more than half of the women in the US have hallux valgus, which is often the result of wearing tight, narrow, or high heeled shoes.[13] It is believed that some individuals have predisposing factors, making their feet more prone to develop hallux valgus. In the progression of hallux valgus, the first MTP joint may become unbalanced, forcing the metatarsal head laterally, causing chronic inflammation and eroding the joint capsule.[11]

Current Treatment Options

Treatment options for first MTP joint OA may depend upon the severity of symptoms a patient is experiencing. Patient symptoms and level of function in conjunction with radiographic evaluation

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[4] Allen LR, Flemming D, Sanders TG. Turf Toe: Ligamentous Injury of the First Metatarsophalangeal Joint. Military Medicine. 2004 November;169(11):xix-xxiv.

[5] Bennett GL, Kay DB, Sabatta J. First Metatarsophalangeal Joint Arthrodesis: An Evaluation of Hardware Failure. Foot & Ankle International. 2005;26(8):593-596.

[6] Shereff MJ, Baumhauer JF. Current Concepts Review Hallux Rigidus and Osteoarthritis of the First Metatarsophalangeal Joint. Journal of Bone and Joint Surgery. 1998;80A(6):898-908.

[7] Moskowitz RW, Altman RD, Hochberg MC, Buckwalter JA, Goldberg VM. Osteoarthritis Diagnosis and Medical Surgical Management 4th ed. Philadelphia: Lippincott Williams & Wilkins; 2007.

[8] Ettl V, Radke S, Gaertner M, Walther M. Arthrodesis in the Treatment of Hallux Rigidus. International Orthopaedics (SCIOT). 2003;27:382-385.

[9] Coughlin MJ, Shurnas PS. Hallux Rigidus Grading and Long-Term Results of Operative Treatment. Journal of Bone and Joint Surgery. 2003;85A(11):2072-2088.

[10] Lombardi CM, Silhanek AD, Connolly FG, Dennis LN, Keslonsky AJ. First Metatarsophalangeal Arthrodesis for Treatment of Hallux Rigidus: A Retrospective Study. 2001;40(3):137-143.

[11] Mann RA, Coughlin MJ, DuVries HL. Hallux Rigidus A Review of the Literature and a Method of Treatment. Clinical Orthopaedics and Related Research. 1979;142:57-63.

[12] Mann RA, Coughlin MJ. Hallux Valgus – Etiology, Anatomy, Treatment and Surgical Considerations. Clinical Orthopaedic and Related Research. 1980 June;157:31-41.

[13] http://orthoinfo.aaos.org/topic.cfm?topic=A00155

should be considered to determine the best treatment option. Non-operative and operative treatments are available.[14]

- Non-Operative Treatments
  Conservative management of first MTP joint OA is typically the first line of treatment for patients. It can include the use of orthotics or accommodative footwear, using a stiff soled shoe, the use of pain relievers and anti-inflammatory medicines, injections, hot/cold temperature baths, and limitations in activities. If conservative treatment fails to relieve symptoms, surgical treatment is recommended.[4,15,16]

- Operative/Surgical Treatments
  Surgical treatments for first MTP joint OA are often divided into joint salvage and joint destructive procedures. Several factors should be considered when selecting the appropriate surgical treatment for a patient with first MTP OA. Age, activity level, severity of disease found upon clinical and radiographic findings, and comorbidities should all be taken into account.[15]

  - Cheilectomy
  - Hemiarthroplasty
  - Total Joint Replacement
  - Arthrodesis
  - Resurfacing/Focal Chondral Defect Repair of the First MTP Joint

The Cartiva Implant was evaluated as a potential alternative treatment for the Indication for Use stated above for which degenerative or post-traumatic arthritis exists in the first MTP in the presence of good bone stock. MTP implant devices, such as the Cartiva, are placed into the metatarsal head in the first MTP joint via press fit implantation. The intent of these devices is to replace focal areas of painful damaged cartilage thereby reducing pain and maintaining range of motion in the MTP joint.

6. NON-CLINICAL EVALUATION OF THE CARTIVA IMPLANT

6.1 Non-Clinical Testing

The following non-clinical testing has been conducted and repeated on worst-case design iterations of the Cartiva Implant:

- Multi-Use Testing
- Confined Compression (new and accelerated aged implants)
- Unconfined Compression (new and accelerated aged implants)
- Creep
- Shear (new and accelerated aged implants)
- Pushout Testing

[14] Ketz J, Baumhauer J, Nawoczenski D. Kinetic and Kinematic Changes in the First Metatarsophalangeal Joint After Cheilectomy. Techniques in Foot and Ankle Surgery. 2006;5(4):266-271.
[15] http://orthoinfo.aaos.org/topic.cfm?topic=A00168
[16] Yee, GY, Lau J. Current Concepts Review: Hallux Rigidus. Foot & Ankle International. 2008;29(6):637-646.

- Hydration Properties
- S-N Analysis
- Fatigue
- Wear (performed on the pure resin, non-sterile Implant, sterilized Implant and sterilized-fatigued Implant devices)
- Chemical Characterization (performed on the pure resin, non-sterile Implant, sterilized Implant and sterilized-fatigued Implant devices)
- Goat Implantation Study
- Rabbit Particulate Implantation Study

No significant concerns were identified in any of these non-clinical tests, and there are no non-clinical concerns being brought to the Panel.

6.2 Biocompatibility

The Cartiva Implant is manufactured from polyvinyl alcohol and saline. In accordance with International Organization for Standardization (ISO) 10993 part 1, such artificial cartilage implants are in contact with bone and or/tissue, with a permanent duration of contact (> 30 days). For this type of product, CDRH recommends the following biocompatibility tests be considered: cytotoxicity, sensitization, irritation (or intracutaneous reactivity), material mediated pyrogenicity, acute systemic toxicity, subchronic toxicity, implantation, chronic toxicity, genotoxicity (mutagenic and clastogenic testing) and carcinogenicity.

The following biocompatibility testing, as per ISO 10993, has been conducted on the Cartiva:

- Cytotoxicity - L929 MEM Elution & Direct Contact
- Sensitization
- Irritation/Intracutaneous
- Acute Systemic Toxicity
- Subchronic Toxicity
- Chronic Toxicity
- Genotoxicity – Amex Reverse Mutation, Chromosomal Aberration Assay, Rodent Bone Marrow Micronucleus Assay
- Implantation
- Pyrogenicity

No significant concerns were identified in the biocompatibility testing provided.

7. CLINICAL STUDY OVERVIEW

7.1 Pivotal Study Investigational Plan (Study Design)

The sponsor conducted the MOTION study in the United Kingdom and Canada. Their clinical protocol is outlined below with notes at the bottom of pertinent sections to outline the study design considerations for each section.

7.1.1 Study Objectives

The study was intended to compare the safety and effectiveness of the Cartiva™ Synthetic Cartilage Implant to an arthrodesis control in the treatment of first metatarsophalangeal joint osteoarthritis.

The study hypothesis was that the Cartiva device would be non-inferior to conventional fusion of the first metatarsophalangeal joint in the identified subjects. Non-inferiority was to be demonstrated in the primary composite endpoint, which included measures of pain and function and if subjects underwent a secondary surgery or undesirable radiographic outcomes.

If non-inferiority was demonstrated, then a superiority analysis was conducted. Patients with secondary procedures (revision surgery) were counted as both effectiveness failures and safety failures (secondary subsequent surgical interventions (SSSI)).

7.1.2 Study Design

The clinical study was designed as a prospective, randomized (2:1), controlled, multicenter, non-inferiority study with two treatment arms. The active treatment arm received a Cartiva™ Synthetic Cartilage Implant and the control arm had arthrodesis. The PMA evaluated Effectiveness at 12 months. Based on our previous feedback, 24 month data and analyses were requested, post-hoc.

7.1.3 Enrollment Criteria (Inclusion/Exclusion Criteria)

Listed below in Table 1 are the enrollment criteria as defined in the sponsor's protocol.

Table 1: Inclusion/Exclusion Criteria

Inclusion Criteria	Exclusion Criteria
Subjects must meet ALL of the following criteria to be eligible to participate in the clinical study: •≥18 years of age; •Degenerative or post-traumatic arthritis of the first metatarsophalangeal joint and is a candidate for arthrodesis with Grade 2, 3, or 4[17] •Preoperative VAS Pain score of ≥40; •Presence of good bone stock, with <1cm osteochondral cyst and without need for bone graft; •Capable of completing self-administered questionnaires; •Be willing and able to return for all study-related follow up procedures;	Subjects may not participate in the clinical study if they meet ANY of the following criteria: • <18 years of age; • Degenerative or post-traumatic arthritis of the first metatarsophalangeal joint and is not a candidate for arthrodesis with Grade 0 or 1 • Preoperative VAS Pain score <40; • Active bacterial infection of the foot; • Additional ipsilateral lower limb (hip, knee, ankle, or foot) pathology that requires active treatment (*i.e.,* surgery, brace); • Bilateral degenerative or post-traumatic arthritis of the first metatarsophalangeal joints that would require simultaneous treatment of both MTP

[17] Coughlin MJ, Shurnas PS. Hallux rigidus. Grading and long-term results of operative treatment. American Journal of Bone Joint Surgery. 85-A(11):2072-88. November 2003

• Have not participated in any other research protocol within the last 30 days, and will not participate in any other research protocol during this study; • If female, is either using contraception or is postmenopausal, or male partner is using contraception; and • Have been informed of the nature of the study, agreeing to its requirements, and have signed the informed consent approved by the IRB/Ethics Committee.	joints; • Previous cheilectomy resulting in inadequate bone stock; • Inflammatory arthropathy; • Diagnosis of gout; • Any significant bone loss, avascular necrosis, and/or large osteochondral cyst (>1cm) of the first metatarsophalangeal joint; • Lesions greater than 10mm in size; • Hallux varus to any degree or hallux valgus >20°; • Physical conditions that would tend to eliminate adequate implant support (*e.g.*, insufficient quality or quantity of bone resulting from cancer, congenital dislocation, or osteoporosis), systemic and metabolic disorders leading to progressive deterioration of bone (*e.g.*, cortisone therapies or immunosuppressive therapies), and/or tumors and/or cysts >1cm of the supporting bone structures; • Patient is on chronic anticoagulation due to a bleeding disorder or has taken anticoagulants within 10 days prior to surgery; • Patient was diagnosed with cancer in the last two (2) years and received treatment with chemotherapy or received radiation to the lower extremity to be treated with Cartiva or arthrodesis; • Suspected allergic reaction to polyvinyl alcohol; • Muscular imbalance, peripheral vascular disease that prohibits adequate healing, or a poor soft-tissue envelope in the surgical field, absence of musculoligamentous supporting structures, or peripheral neuropathy; • In the opinion of the Investigator, any medical condition that makes the subject unsuitable for inclusion in the study, including, but not limited to patients with a diagnosis of concomitant injury that may interfere with healing; patients with clinically significant renal, hepatic, cardiac, endocrine, hematologic, autoimmune or any systemic disease or systemic infection which may make interpretation of the results difficult; patients who have undergone systemic administration within 30 days prior to implantation of any type of corticosteroid, antineoplastic, immunostimulating or

	immunosuppressive agents; • Co-morbidity that reduces life expectancy to less than 36 months; • If female, be pregnant, planning to become pregnant during the course of the study, breast-feeding, or if childbearing age, is not using contraception; • History of substance abuse (e.g. recreational drugs, narcotics, or alcohol); • Is a prisoner or ward of the state; • Are unable to meet the treatment and follow up protocol requirements; or • Are being compensated under workers' compensation or are currently involved in litigation.

7.1.4 Control Treatment

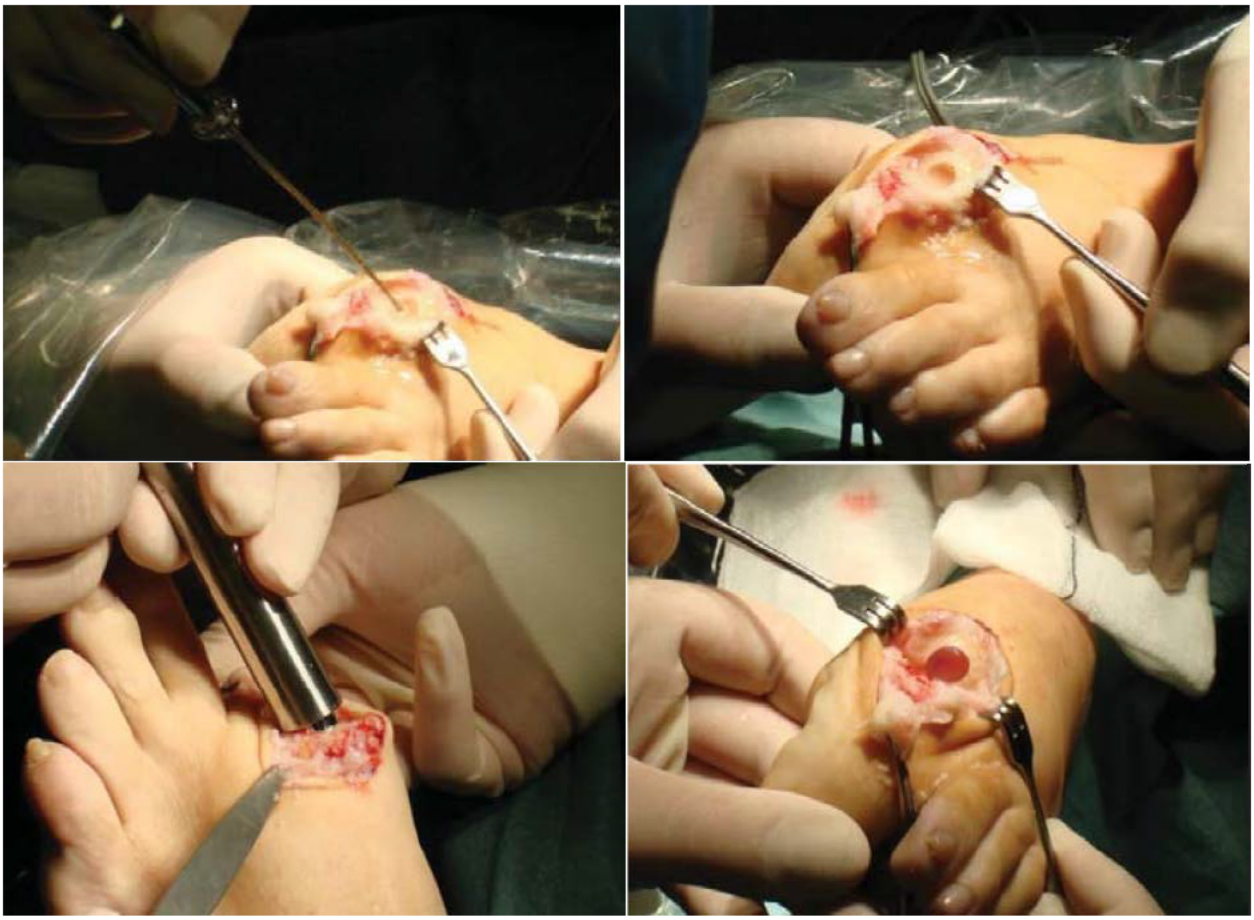
The sponsor instructed the investigators to utilize their standard surgical technique for all arthrodesis subjects. The following standard aseptic preparation of the subject for surgery and surgical steps may include the following:

- Using standard surgical technique, access the affected first MTP joint.
- Resect any osteophytes as needed from the proximal phalanx and the distal metatarsal.
- Ensure proper alignment and angle/degree of the joint prior to placement of hardware.
- Use screws and/or plates, as necessary, to fuse the joint.
- Repair any soft tissue, as necessary, and close the surgical wound in standard fashion.

7.1.5 Surgical Procedure Used to Implant the Investigational Device

The Cartiva procedure is similar to that used for osteochondral autograft or allograft transplantation; the Cartiva Implant is placed into a pre-drilled hole to resurface the damaged area of cartilage/bone. A small straight dorsal or straight medial incision approximately 4cm long is made along the dorsal or medial aspect of the first MTP joint to provide exposure of the capsule. Osteophytes are resected from the proximal phalanx and/or metatarsal head. Ability to attain over 40 degrees of dorsiflexion prior to insertion of Cartiva is preferred. The concave end of the Placer is used to identify the target implantation site. A guide pin and drill is used to make the metatarsal head defect site. The Introducer tube is used to introduce the implant to the site. The Placer is then used to press fit the implant into the metatarsal head defect. Surgeons are then instructed to resect any osteophytes from dorsal, lateral, and medial aspects of the metatarsal head. Images of the site preparation, Head Defect, Implant Placement, and Insertion of the Cartiva device are shown in Figure 3 below.

Figure 3: Site Preparation, Head Defect, and Insertion of Cartiva implant (from left to right)



After the operation, subjects receiving Cartiva were to have their operative site bandaged and the treated foot placed in a stiff soled shoe. Weight bearing could begin immediately as tolerated by the subject. Range of motion exercises are encouraged immediately to avoid stiffness.

Subjects treated with Arthrodesis were to have their wound bandaged and treated foot placed in a dressing, walking boot or cast for a length of time as determined by the Investigator. Full weight bearing and any rehabilitation were to occur after union, confirmed by x-ray, or at the discretion of the treating Investigator.

7.1.6 Assessment Instruments and Follow-Up Schedule

Table 2 below outlines the assessments planned for each follow-up visit.

Table 2: Patient Assessment Schedule

Data Required	Screening /Baseline	Operative/ Discharge Day 0	2-week Follow Up (±7days)	6-week Follow Up (±14 days)	3-month Follow Up (±14 days)	6-month Follow Up (±14 days)	12-month Follow Up (±14 days)	18-month Follow Up (±14 days)	24-month Follow Up (±14 days)	Unscheduled Visit
Informed Consent	X									
I/E Criteria	X									
Medical History	X									

Foot Exam	X		X	X	X	X	X		X	X
Foot X-ray	X		X	X	X	X	X		X	X
General Health	X		X	X	X	X	X		X	X
VAS Pain	X		X	X	X	X	X		X	X
Foot Function Index Revised (FFI-R)	X		X	X	X	X	X		X	X
Foot & Ankle Ability Measure (FAAM)	X		X	X	X	X	X		X	X
SF-36 Health Survey	X			X	X	X	X		X	X
Global Assessment (Subject & Site PI)			X	X	X	X	X		X	X
Operative/ Discharge Form		X								
Follow Up Visit Form			X	X	X	X	X		X	X
Telephone Follow-up								X		
AE Reporting		X	X	X	X	X	X	X	X	X

7.1.7 Primary Effectiveness Endpoint and Study Success

The primary objective of the study was to show the overall success rate in the investigational treatment group to be statistically non-inferior to the success rate in the control (arthrodesis) group for both the primary effectiveness endpoint at 12 months after surgery and the primary safety endpoint at 24 months. The data in the submitted PMA evaluated effectiveness at 12 months; based on the Agency's previous feedback, a post-hoc 24 month effectiveness analysis was requested and provided.

The primary endpoint, as originally specified by the sponsor, consists of a single composite primary endpoint reflecting three study outcomes (pain, function, and safety). The individual subject's outcome is considered a success if all of the following criteria are met:

- Improvement (decrease) from baseline in VAS Pain of ≥30% at 12 months;
- Maintenance of function from baseline in FAAM Sports score at 12 months (inclusive of a decrease <9); and
- Freedom from the events listed below for the respective treatment arms and freedom from subsequent secondary surgical interventions for both treatment arm to include revisions, removals, reoperations and/or supplemental fixations over the time period of 24 months from surgery.
- No radiographic failure, which for each arm is defined separately:
    - Cartiva - device displacement, device fragmentation and/or development of avascular necrosis
    - Arthrodesis - mal-union, non-union and/or hardware failure. The radiographic assessment for non-union and mal-union will only be included from 3 months to 24 months after surgery.

The proportion of successes in each group was determined, and the difference (Cartiva minus arthrodesis) and one-sided 95% confidence interval for the difference between treatment groups was

calculated. If the one-sided 95% lower confidence interval is greater than the equivalence limit (-15%), the primary endpoint will have been met.

In its feedback to the sponsor prior to the study, the Agency requested that the analysis of study success be performed at 24 months instead of 12 months on the basis that 24 months would be needed to adequately assess longer-term adverse events and more reliably determine fusion and other clinical outcomes. In its review of the PMA, the Agency noted that the sponsor had utilized the Foot and Ankle Measure (FAAM) Sports Subscale in the primary effectiveness analysis for the device in lieu of the FAAM Activities of Daily Living (ADL) primary effectiveness measure previously proposed by the sponsor prior to conducting the oUS the study. FDA requested the sponsor provide post-hoc analyses in which the effectiveness endpoint be evaluated at 24 months and utilize the FAAM ADL effectiveness measure. The sponsor provided these analyses in its response. (Note: As will be shown later, these changes are slightly less conservative or more favorable to Cartiva.)

In addition, in feedback provided to the sponsor prior to the study, the Agency recommended the use of a non-inferiority margin corresponding to a maximum clinically insignificant difference in lieu of the 15% non-inferiority margin proposed by the sponsor. The sponsor utilized a 15% margin in its PMA based, in part, on the following: "[t]he clinicians involved in the study design, took into consideration the patient population, the types of responses that are expected for Arthrodesis and felt that a 15% delta between the study groups would was appropriate given the potential benefits of Cartiva and was a clinically insignificant difference. In particular, the potential for a Cartiva patient's ability to maintain motion of the joint, quicker rehabilitation, less restrictive post-operative instructions, quicker return to function and sports activity and the impact these have on their quality of life would allow for efficacy (-15%) and not be unacceptably worse than arthrodesis."

The Panel will be asked to comment on the appropriateness of the sponsor's chosen 15% non-inferiority margin for its clinical study. If the Panel does not believe this margin to be appropriate, the Panel will be asked to recommend a non-inferiority margin that it believes to be appropriate.

7.1.8 Secondary Effectiveness Endpoints

Secondary endpoints for effectiveness include clinical assessments, functional assessments, and quality of life measurements as follows:

- VAS Pain;
- FAAM Activities of Daily Living (ADL) Score (Time to return to function as measured by the FAAM ADL Score will be evaluated and compared between groups to evaluate the perceived benefit of Cartiva subjects to return to activities of daily living more quickly than arthrodesis subjects.);
- FAAM Sports
- MTP joint motion per goniometer measurements;
- Subject Global Assessment;
- Investigator Global Assessment;
- SF-36 Physical Functioning Scale; and
- Foot Function Index Revised (FFI-R).

The sponsor pre-specified that each secondary variable were to be tested in the following order:
1. VAS Scores
2. FAAM Activities of Daily Living Scores
3. Active MTP Peak Dorsiflexion
4. Patient Global Assessment
5. Investigator Global Assessment
6. SF-36 Physical Functioning Scale
7. Foot Function Index Revised (FFI-R)

According to this analysis plan, if the first secondary endpoint is not significant then additional secondary endpoints will not be tested. Thus, if Cartiva was not shown to be significantly better in terms of VAS scores, then claims regarding other secondary endpoints, such as Active MTP Peak Dorsiflexion, would not be allowed. The purpose of pre-specifying a plan such as this one is to control Type I error when multiple endpoints are tested. It would be statistically inappropriate to test all of the secondary endpoints and then decide afterwards which one is the most important, as this inflates the Type I error rate.

After completing the study, the sponsor explored other methods of analyzing secondary endpoints, such as using a Hochberg step-down analysis and using a Bonferroni adjustment. While these methods would have been appropriate if they had been pre-specified, they were used post-hoc and as such, are subject to bias.

7.1.9 Subgroup Analysis

Analysis was also conducted on the following subgroups:

- Gender;
- Grade of OA (2, 3, or 4)
- Implant size (8 mm or 10 mm)
- BMI (≥ 30 or <30)
- VAS Pain score at baseline (≤50 or >50);
- Regular activity (Yes or No); and/or
- Age (≤65 years or >65 years).

7.2 Statistical Analysis Plan

7.2.1 Randomization

The initial two subjects enrolled at each site (except for Site 2) were non-randomized and implanted with Cartiva for the purpose of site training. These subjects are called Roll-In subjects and are only included in safety analyses, not in effectiveness analyses.

The subjects were randomized 2:1 with implantation with Cartiva in the active treatment arm, or arthrodesis in the control arm, respectively.

7.2.2 Planned and Actual Sample Size Calculation

The sponsor originally assumed they would need 171 subjects, 114 Cartiva subjects and 57 Arthrodesis subjects. These estimates were based on assumptions of 80% power, one-sided alpha=0.05, a 15% non-inferiority margin, 60% response rate for arthrodesis and 64% for Cartiva. After incorporating a 20% dropout rate, 143 and 71 subjects (214 total) were needed for the Cartiva and arthrodesis group, respectively.

The sample size was increased to 249 subjects to include non-randomized roll-in subjects. By 2010, the sample size was revised again to 230 subjects. (Note: There was an interim analysis conducted to determine if the sample size needed to be changed. None of these changes happened because of the interim analysis. The details of the interim analysis are in the next section, but the Agency has no concerns regarding this analysis.) In the end, 236 subjects were enrolled, 202 subjects were treated (including roll-in subjects), and 180 subjects were randomized and treated.

7.2.3 Interim Analysis

As pre-specified in the May, 2012 SAP, one interim analysis was conducted once 1/3 of the planned number of subjects were enrolled, randomized, and followed for 12 months to evaluate sample size assumptions. The percentage of subjects meeting the success criteria was calculated for each treatment arm. Percentages from the ITT and the mITT populations and from the Worst Case and Completer sensitivity analyses were calculated.

Although the goal of the interim analysis was not to stop the study prematurely, an adjustment to the overall alpha level was performed. The group sequential design by Peto (Geller and Pocock, 1987) was used for controlling the overall type I error rate or alpha level. Based on this method, 0.001 of the total alpha level was attributed to the interim analysis even though no statistical testing was performed. Per this group sequential methodology, an alpha level of 0.050 was used at the final analysis.

The June, 2012 interim analysis to confirm the sample size assumptions was completed as pre-specified in the original SAP dated May 2012 without deviation. A total of seventy-five subjects who were screened and randomized into the trial were included in this interim analysis. While the actual treatment response rates (Cartiva 82%, control 76%) are significantly higher than were expected (Cartiva 64%, control 60%), the observed between-treatment difference (6%) was very close to what was expected (4%). No sample size adjustment was recommended, and therefore no adjustment to the sample size was made.

7.2.4 Length of Treatment and Follow-up

Subjects were followed-up at 2 and 6 weeks, 3, 6, 12, and 24 months post-treatment.

7.2.5 Blinding

Subjects, investigators, and independent radiographic reviewers were not blinded to the treatment assignment.

7.2.6 Analysis Populations

The table below shows all of the different analysis populations, explains what they are, and shows how many subjects are in each.

Table 3: Study Population Statistical Analysis [FDA Table]

Population	Description	N		
		Cartiva	Arthrodesis	Total
Intent-to-Treat (ITT)	The ITT population includes all randomized subjects, irrespective of treatment compliance. No data will be excluded due to protocol deviations. Values for missing efficacy data will be imputed using the method of last observation carried forward (LOCF).	132	65	197
Modified Intent-to-Treat (mITT)	The mITT population includes all randomized subjects who receive treatment. Data from subjects who were randomized but never underwent study treatment will be excluded. Values for missing efficacy data will be imputed using the method of last observation carried forward (LOCF)(original analysis).	130	50	180
Completed Cases Population (CC)	The completed cases (CC) population will include all randomized subjects who receive treatment and who have follow-up, through the time of endpoint analysis (minimum 24* months).	129**	47	176
Per Protocol Population (PP)	The per-protocol (PP) population will include all randomized subjects who receive treatment and who have follow-up through the time of endpoint analysis (minimum 12 months). The population will exclude all subjects not treated as randomized and subjects having major protocol deviations.*** There will be no data imputation for missing data.	122	46	168
Safety Population	The safety population will include all treated subjects as they were treated.	152	50	202
FDA Amended PP	The FDA amended PP population includes all patients with major protocol deviations removed. Major protocol deviations are provided in section 8.3 below.	107	41	148

*originally required minimum 12 months

** includes one subject that had 24 month VAS and FAAM scores but left before getting radiographs, the subject was deemed a success

***The FDA does not agree with the sponsor's definition of a major protocol violation. The numbers presented here are according to their original submission definitions (12 months). Sensitivity analyses with different numbers of subjects are provided below.

8. CLINICAL STUDY RESULTS

8.1 Subject Accounting

The prospective, randomized controlled clinical trial included a total of 236 patients enrolled from 12 clinical study sites in the United Kingdom and Canada. Of those 236 enrolled, 197 were randomized and

22 were non-randomized. By definition, the ITT population consists of 197 all-randomized patients (132 investigational and 65 controls).

The mITT population, submitted by the sponsor for the PMA consists of 180 patients (197 patients in the ITT group minus an additional 17 subjects excluded who never underwent treatment) divided into 130 investigational and 50 controls. The PP population (168 subjects (122 Cartiva and 46 Arthrodesis)) excluded subjects who were not treated as randomized and those with "major" protocol deviations (n=6).

The Safety population is the subset of all enrolled subjects (236) minus 34 withdrawals prior to (17) and after (17) randomization, leaving 202 subjects who were actually treated with either the Cartiva device or arthrodesis (152 Cartiva and 50 Arthrodesis).

The reasons subjects withdrew prior to randomization and post-randomization but prior to treatment are provided in the tables below.

Table 4: Withdrawals Pre-Randomization [CARTIVA Table]

Pre-Randomization Withdrawal Reason	N=17 (% of 17)
Did not meet inclusion/exclusion criteria	2
Investigator withdrew patient	1
Patient voluntarily withdrew	13
Patient was not consented to study	1
Total Subjects Withdrawn Prior to Randomization	**17**

Table 5: Withdrawals Post-Randomization [CARTIVA Table]

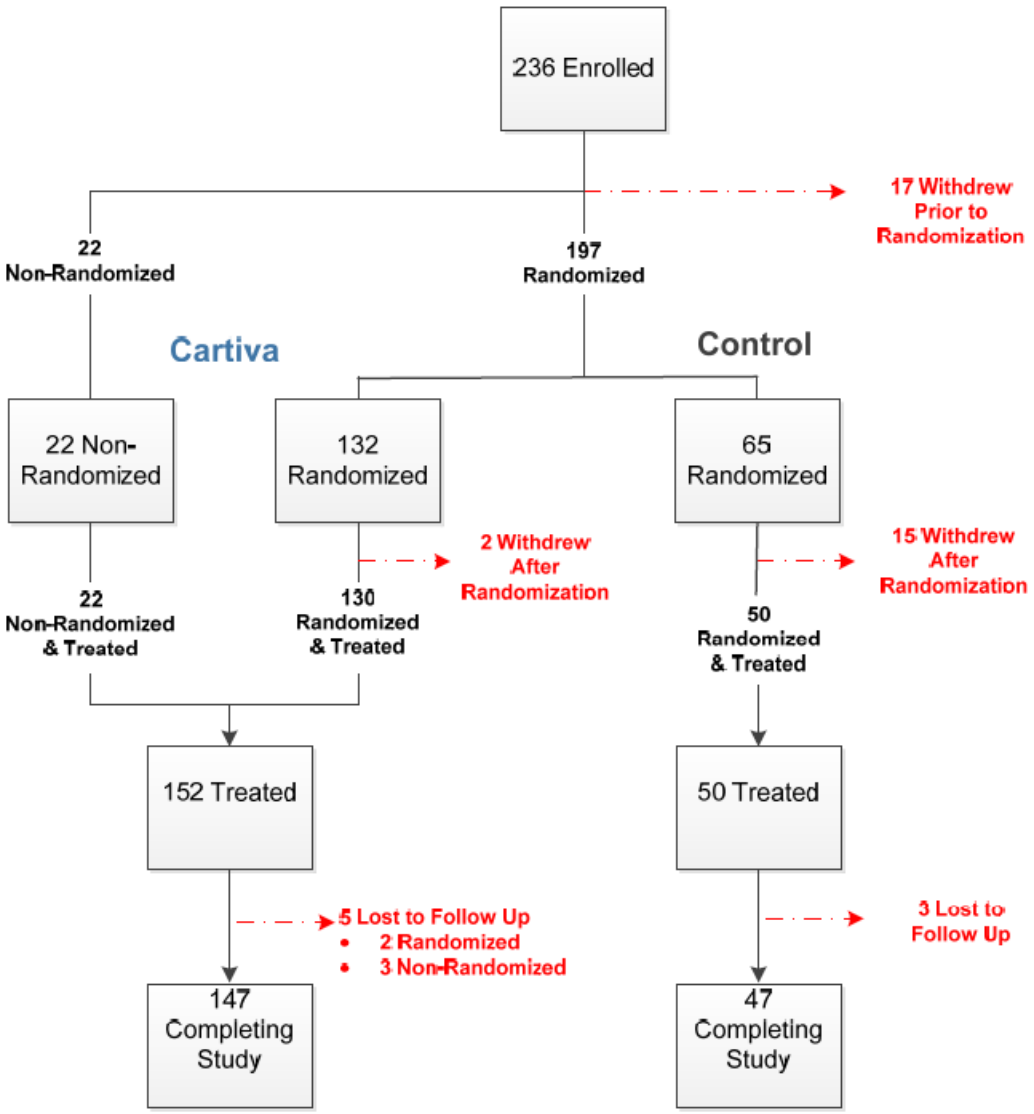
Post-Randomization Withdrawal Reason	Cartiva	Arthrodesis	N=17 (% of 17)
Subject wanted investigational device		10	59%
Subject wanted fusion	1		6%
Subject wanted fusion closer to home		2	12%
Not enough time to prepare for fusion surgery		1	6%
Investigator withdrew subject due to subject requesting multiple fusions at time of surgery		1	6%
Subject elected for cheilectomy		1	6%
Subject withdrew due to personal circumstances	1		6%
Total Subjects Withdrawn After Randomization/Prior to Treatment	**2**	**15**	**17**

In a study randomized 2:1, Cartiva to Arthrodesis, many subjects were expecting to be randomized to Cartiva. Consequently, 10 subjects withdrew when they were randomized to Arthrodesis because they

had been hoping to be randomized to Cartiva, as compared to one that withdrew because the subject had been hoping to be randomized to fusion.

The subject accounting can be seen in Figure 4 below. There is one clarification; Figure 4 indicates that 2 randomized Cartiva subjects were lost to follow-up. One of these subjects had an SSSI prior to study exit, was considered a failure on the primary endpoint, and therefore is not considered missing for the primary analysis..

Figure 4: Cartiva Patient Accounting Table



Only 4 (2.2%) randomized and treated subjects were lost to follow-up. The sponsor is to be commended for the low loss to follow-up among treated subjects.

8.2 Missing Data

The sponsor originally planned to use the ITT population and impute missing data using Last Observation Carried Forward. As 15 arthrodesis subjects (23%) withdrew between randomization and treatment, using the ITT population would mean imputing data for 28% of the subjects. Using the LOCF approach, all 15 of the subjects that withdrew prior to treatment would have been classified as failures. The sponsor and the FDA agreed that this approach was unreasonable. Multiple imputations is a more reasonable approach for dealing with this type of missing data, and this was explored. However, imputing large portions of the data for subjects that were never treated was not very instructive for this situation. Using multiple imputations to impute data for untreated subjects can be instructive if there are big differences in the baseline covariates between the treated and untreated subjects, specifically covariates that might be strong predictors of success or failure. When the original multiple imputations was done, the sponsor concluded that there were no such differences, and FDA agreed with this conclusion.

There were 4 subjects (1 Cartiva, 3 Arthrodesis) that did not complete the study or could not be evaluated for the primary endpoint. They had various levels of follow-up.

Table 6: Subjects that dropped out before they could be determined to be a success or failure [FDA Table]

Subject*	Treatment Group	Last Follow-up	% Improve-ment in VAS	Improvement in FAAM ADL	SSSI	Radiographic Success
1	Arthr.	3-months	--**	--**	No	Yes
2	Arthr.	6-months	99%***	--***	No	Yes
3	Arthr.	3-months	76%	20	No	Yes
4	Cartiva	1 year	98%	19	No	Yes

* Subject IDs were redacted throughout in order to protect patient privacy

**Subject 1 has no post-baseline VAS or FAAM ADL scores, only X-rays.

***Subject 2 did not have baseline FAAM ADL or any VAS or FAAM past 6 weeks, but at 6 weeks the FAAM ADL was 90 and the VAS was 1.

There are no data that would suggest that any of these subjects would have been failures if they had completed the study.

The sponsor and FDA decided to focus on the mITT population, which includes only those subjects that were randomized and treated. Because there is a limited amount of missing data among this population, most of the tables and analyses presented are based on the completers or those that have an observation at a given time point. Data is not imputed unless it is specifically noted.

8.3 Protocol Deviations

The sponsor originally reported a total of 463 protocol deviations, occurring in 174 subjects across 12 study sites. These occurred in 39 (78%) of the arthrodesis and 135 (89%) of the Cartiva subjects. The majority of the deviations were determined for visits outside the window (48%), assessments not performed per protocol (20%) or Investigator/site omission (13%).

Of the 463 deviations, 6 deviations in 4 subjects were determined by the sponsor to be "Major". These were broken down into 4 Cartiva subjects and 0 Arthrodesis subjects who were outside the window ± 60 days for follow-up. There was one Cartiva and one Arthrodesis subject who had taken pain medication "within 8 hours at 1 year assessment". These 6 subjects were removed from the PP analysis.

The sponsor and FDA determined that the following types of deviations would be classified as major: Subject not consented; Inclusion/Exclusion Criteria Violations; subject not capable of completing questionnaires; subject participated in research in past 30 days; active infection of foot; previous cheilectomy; significant bone loss; suspected allergic reaction to PVA; muscular imbalance; in opinion of Investigator subject was not suitable for treatment; baseline, 12 or 24 follow-up visits conducted by Investigator not trained on protocol; follow-up visit not within ± 60 days at 12 and 24 months; and subject took pain medication within 8 hours of the baseline or 12 month assessment. All other deviations were considered as "Minor", because, according to the sponsor, they did not "have an impact on the assessment of the primary endpoint".

The FDA also considers the sponsor's listed deviations to be major, as well.

Table 7: Previous MOTION Study Deviations Table (n=463) [CARTIVA Table]

Deviation Type	Cartiva (n=152)	Arthrodesis (n=50)	Total Deviations (n=202)	Major Deviation (n=202)
Follow up visit out of visit window	177 (47%)	43 (49%)	220 (48%)	4 (67%)
Follow up @ 12 & 24 Mo >±60 days	*4*[2]	*0*	*4*	*4*[2]
Follow up out of window with no impact on endpoint assessment	*173*	*43*	*216*	*0*
Assessments not performed per protocol	77 (21%)	17 (20%)	94 (20%)	0
Investigator/Site oversight or omission	51 (14%)	7 (8%)	58 (13%)	0
Consent form deviation	19 (5%)	4 (5%)	23 (5%)	0
Subject took pain medication within 8 hours of completing assessments	16 (4%)	8 (9%)	26[1] (6%)	2 (33%)
Pain Med w/in 8 hrs. @ 12 Mo.	*1*[3]	*1*[4]	*2*	*2*
Pain Med w/in 8 hrs. other visits	*15*	*7*	*24*	*0*
Eligibility Criteria Not Met	13 (3%)	3 (3%)	16 (3%)	0
Other	14 (4%)	2 (2%)	16 (3%)	0
Randomization >72 hrs. before surgery	6	1	7	0
Other deviations	8	1	9	0

Follow up visit not completed	7 (2%)	3 (3%)	10 (2%)	0
TOTAL	**374**	**87**	**463**	**6**

[1]Two subjects (b) (5) took medication within 8 hours of baseline assessment.
[2]Subjects (b) (5)
[3]Subject (b) (5)
[4]Subject (b) (5)

After elimination of duplicate protocol deviation listings, there are a remaining total of 416 individual protocol deviations that occurred during the MOTION study (rather than the total of 463 originally reported in the PMA). The table below demonstrates how the 416 total deviations from 202 subjects were divided into study group, type, and determination of major deviation status.

Table 8: MOTION Study Deviations (n=416) [CARTIVA Table]

Deviation Type	Cartiva® (n=152)	Fusion (n=50)	Total Deviations (n=202)	Major Deviation PP1 (n=202)	Major Deviation PP2[2] (n=202)
Follow up visit out of visit window *Follow up @ 24 Mo > -60 days* *Follow up out of window with no impact on endpoint assessment*	168 (51%) *2* *166*	42 (49%) *0* *42*	210 (50%) *2* *208*	2 (1.0%) *2* *0*	0 (0%) *0* *0*
Assessments not performed per protocol	71 (22%)	17 (20%)	88 (21%)	0	0
Investigator/Site oversight or omission	41 (12%)	5 (6%)	46 (11%)	0	0
Consent form deviation	13 (4%)	3 (4%)	16 (4%)	0	0
Subject took pain medication within 8 hours of completing assessments *Pain Med w/in 8 hrs. @ 24 Mo.* *Pain Med w/in 8 hrs. other visits*	15 (5%) *0* *15*	8 (9%) *0* *8*	23 (6%)[1] *0* *23*	0 *0* *0*	0 *0* *0*
Inclusion/Exclusion Eligibility Criteria Not Met[3]	8 (2%)	5 (6%)	13 (3%)	0	2
Other *Randomization >72 hrs. before surgery* *Other deviations*	10 (3%) 5 5	2 (2%) 2 0	12 (3%) 7 5	0 0 0	0 0 0
Follow up visit not completed	5 (2%)	3 (4%)	8 (2%)	0	0
TOTAL **% Deviations by Subjects**	**331 (218%)**	**85 (166%)**	**416[1] (206%)**	**2 (0.5%)**	**2 (0.5%)**

[1] Subject (b) (5) not assigned a treatment group.
[2] Per protocol analysis conducted at FDA's request.

A breakdown of protocol violations according to the treatment group reveals that there was a 6% greater number of protocol deviations related to Investigator/Site oversight or omission in the Cartiva group than in the control group. These Major deviations were for out-of-window (OOW) and the use of pain meds at the 12-month follow-up assessment. However, individual subjects with deviations who failed Inclusion/Exclusion criteria, or others OOW, could also significantly impact an assessment of safety and effectiveness for the device.

FDA reviewed the deviations of each individual and considered them by type, and the major or minor impact on assessing individual outcome. Based upon the definitions of major protocol deviations described above in FDA's analysis of all protocol deviations, there were 28 patients (22 investigational and 6 controls) who should be excluded from the PP study analyses for Major protocol deviations, which when subtracted from the Completed Cases (CC) dataset would result in a PP dataset of (107 investigational and 41 control). Others had pain medication within 8 hours of either a baseline or an endpoint assessment.

8.4 Subject Demographics and Baseline Characteristics

The following tables provide a summary and comparisons of demographic variables and patient preoperative characteristics between the Cartiva™ and Control groups. The typical subject was a female about age 56. The sponsor did not provide an evaluation of preoperative risk factors such as smoking, previous revision surgery, or diabetes.

Table 9: Gender [CARTIVA Table]

Categorical Variables	Cartiva (N=132) x/n (%) (LCL, UCL)[1]	Arthrodesis (N=65) x/n (%) (LCL, UCL)[1]	Overall (N=197) x/n (%) (LCL, UCL)[1]	P-Value[2]
Gender (Male)	27/132 (20.46) (13.93, 28.35)	16/65 (24.62) (14.77, 36.87)	43/197 (21.83) (16.27, 28.25)	0.5827

[1]Exact binomial 95% lower and upper confidence limits.
[2]Two-sided Fisher's exact test.

Table 10: Baseline Demographics ITT Population [CARTIVA Table]

Characteristic Continuous Variables	Cartiva Mean (SD) N Med (Min, Max)	Arthrodesis Mean (SD) N Med (Min, Max)	Overall Mean (SD) N Med (Min, Max)	P-Value[1]
Age	57.02 (8.921) 132 57.6 (30.3, 79.1)	55.52 (10.285) 65 55.7 (29.1, 78.1)	56.53 (9.393) 197 57.3 (29.2, 79.1)	0.3081
Height (ins)	65.32 (3.096) 132 65 (58, 72)	65.97 (3.691) 64[2] 65.4, (60, 75)	65.53 (3.307) 196[2] 65 (58, 75)	0.3472
Weight (lbs)	165.78 (31.988) 132 160.5 (105, 255.7)	165.18 (36.511) 65 157 (110.2, 290.0)	165.58 (33.455) 197 160 (105, 290)	0.6404
BMI	27.22 (4.347) 132 26.5 (19.1, 37)	26.49 (4.787) 64[2] 25.7 (19, 41.6)	26.98 (4.496) 196[2] 26.3 (19, 41.6)	0.1788
VAS	67.84 (13.858) 132 68 (27.8, 100)	69.76 (13.505) 65 70 (38. 97.5)	67.47 (13.738) 197 69 (27.8, 100)	0.3580
FAAM Sports	36.92 (21.064) 130[3] 34.4 (0, 100)	33.84 (19.508) 64[3] 31.3 (0. 87.5)	35.07 (20.564) 194[3] 34.4 (0,100)	0.2139
FAAM ADL	59.06 (17.071) 130[3] 57.9 (7.1, 100)	55.41 (15.883) 64[3] 54.2 (23.8, 95.2)	57.85 (16.736) 194[3] 57.1 (7.1, 100)	0.0780
SF-36 Physical Functioning	52.29 (22.601) 132 50 (0, 100)	48.21 (23.080) 65 40 (0. 100)	50.95 (22.782) 197 50 (0, 100)	0.1651

[1]Two-sided Wilcoxon rank sum test using the Student's t approximation.
[2]Height was not recorded for one arthrodesis patient so height and BMI are missing for that patient.
[3]One patient from each group did not have sufficient responses to score for the FAAM Sports test and two subjects from the Cartiva group and one patient from the Arthrodesis group did not have FAAM ADL scores.

The sponsor also provides analyses of all demographics, which demonstrate that the baseline characteristics were not different for randomized subjects who withdrew prior to treatment compared to those who were treated and remained in the study.

Table 11: Baseline Demographics – Treated vs. Randomized Untreated [CARTIVA Table]

There were only minor differences of < 2 points mean noted between the two treatment groups concerning age, height, weight, BMI, and VAS. The range of scores for VAS at baseline was 27.8 to 100 points for the Cartiva group compared with 38 and 97.5 for the Arthrodesis group. However, this is a protocol violation for those subjects who were enrolled at a Preoperative baseline VAS Pain score <40 and is discussed in the section above.

There was a greater percentage of females enrolled in both groups, with 79.5% for Cartiva (105/132) and 75.3% for the Arthrodesis group (49/65) and > 4% more females in the Cartiva group than in the control group.

The investigational group had a mean age of 57.02 years (range 30.3-79.1) and the control group had a mean age of 55.52 years (range 29.1-78.1). Thus, subjects who received the Cartiva device were, on average, approximately 1½ years older than control patients.

The mean FAAM Sports and ADL and SF-36 Physical Functioning scores at baseline for subjects in the Cartiva group were higher than the mean scores of subjects in the Arthrodesis group by ≥ 3 points.

There were 28% of Cartiva subjects and 33% of Arthrodesis who were enrolled with Grade 2 OA. At the 24-month analysis, Cartiva® patients with Grade 2 osteoarthritis had a greater mean VAS scores (20.6) than those with Grade 3 or 4 osteoarthritis (12.0).

There was a greater percentage of subjects enrolled in the study who had Grade 3 OA in both groups, with 56.06% for Cartiva (74/132) and 45.31% for the Arthrodesis group (29/64), corresponding to > 10% more Grade 3 OA in the Cartiva group than in the control group. There were > 6% more subjects with

Grade 4 OA in the Arthrodesis group. The table below demonstrates subject baseline characteristics for OA Grade in the MOTION Study.

Table 12: MOTION Study Subject Baseline Characteristics – OA Grade [CARTIVA Table]

Categorical Variables	Cartiva (N=132) x/n (%) (LCL, UCL)[1]	Arthrodesis (N=65) x/n (%) (LCL, UCL)[1]	Overall (N=197) x/n (%) (LCL, UCL)[1]	P-Value[2]
OA Grade				0.3418
2	37/132 (28.03)	21/64[3] (32.81)	58/196 (29.59)	
3	74/132 (56.06)	29/64 (45.31)	103/196 (52.55)	
4	21/132 (15.91)	14/64 (21.88)	35/196 (17.86)	

8.5 Surgery and Hospitalization Information

The sponsor provided a summary of the size implants and fixation method used in the Cartiva and Arthrodesis groups, respectively. Of the 152 Cartiva patients, 127 (84%) received a 10mm implant and 25 (16%) received an 8mm implant. Of the 50 patients treated with arthrodesis, 26 (52%) were fused using two cross screws, 21 (42%) were fused using a screw and plating system, and 3 (6%) were fused using two cross screws and a K-wire to achieve fixation.

In its review of the PMA, the Agency requested surgical information on type and length of anesthesia, procedure time, and blood loss between groups. In their response, the sponsor stated that this type of information was not available for all subjects. This is because these items were not considered as data points included for collection on operative Case Report Forms. The percentage of patients for whom this information is available is as follows: length of surgery (Procedure Time) for 74% Cartiva and 78% fusion patients; length of anesthesia for 90% of Cartiva and 88% of fusion patients; and blood loss for 60% Cartiva and 62% fusion patients. The tables below outline the differences seen.

Table 13: Procedure Time and Length of Anesthesia [CARTIVA Table]

	Cartiva®					Fusion				
	N	Mean	Med	Min	Max	N	Mean	Med	Min	Max
Procedure Time	112	35	32	13	80	39	58	55	30	122
Length of Anesthesia	137	67	65	20	176	44	95	90	30	218

Table 14: Anesthesia Type [CARTIVA Table]

	Cartiva® (n=152)		Fusion (n=50)	
Anesthesia Type	N	%	N	%
General	140	92.1	46	92.0
Regional	2	1.3	1	2.0
Local	3	2.0	1	2.0
Not Recorded	7	4.6	2	4.0

The sponsor claims notable benefits of the Cartiva® implant to fusion in length of procedure time (40% reduction) and anesthesia time (30% reduction). It is not clear how to weigh the impact of 25 minutes less time under general anesthesia on the well-being of the subject. Please see a further discussion of proposed device benefits in the Benefit Risk Assessment section.

The sponsor also claims that another benefit for the investigational device is the postoperative recovery from surgery is much shorter than a fusion surgery of the 1st MTP joint. Although they have provided a description of the rehabilitation procedures for each treatment group, there are no formal analyses of time or quality differences. Again, please refer to the further discussion of proposed device benefits in the Benefit Risk Assessment section.

9. SAFETY EVALUATION

The safety of the investigational device for this PMA was assessed as a separate analysis population and was a part of the composite primary study endpoint. Safety for the primary endpoint was assessed by the sponsor as those pre-specified by evaluating adverse events leading to SSSI. Safety for the population was evaluated based on the nature and frequency of adverse events, which occurred in the Cartiva™ group, as compared to those which occurred in the control group.

Adverse events were collected from this population by System Organ Class (SOC) and Preferred Term (PT). There are further subcategories into Treatment and Non-Treatment Emergent, being defined as device or operative related events. The safety population was also assessed for safety related to Radiographic data. There were 318 total adverse events reported. These were further subdivided by severity, resolution status, and unanticipated events.

Table 15: Summary of Adverse Event Experiences- Safety Analysis Set [CARTIVA Table]

	Cartiva (N = 152)			Fusion (N = 50)			Cartiva vs Fusion			
	Events	n	%	Events	n	%	Diff	LB[1]	UB[1]	p-value[2]
Any adverse event	245	105	69.1%	72	36	72.0%	-2.9%	-18.8%	12.9%	0.727
Treatment Emergent Event	102	67	44.1%	32	21	42.0%	2.1%	-14.0%	18.1%	0.870
Device Related Event	31	23	15.1%	4	4	8.0%	7.1%	-9.0%	23.0%	0.238
Operative Procedure Related Event	71	51	33.6%	28	18	36.0%	-2.4%	-18.2%	13.5%	0.864
Non-Treatment Emergent Event	143	73	48.0%	40	26	52.0%	-4.0%	-20.0%	12.2%	0.745
Any Serious adverse event	37	30	19.7%	12	9	18.0%	1.7%	-14.2%	17.5%	0.999
Treatment Emergent Event	17	17	11.2%	4	4	8.0%	3.2%	-12.9%	19.2%	0.605
Device Related Event	11	11	7.2%	2	2	4.0%	3.2%	-12.9%	19.3%	0.526
Operative Procedure Related Event	6	6	3.9%	2	2	4.0%	-0.1%	-16.2%	16.1%	0.999
Non-Treatment Emergent Event	20	14	9.2%	8	5	10.0%	-0.8%	-16.8%	15.2%	0.999
AE by Severity										
Mild	110	70	46.1%	41	25	50.0%	-3.9%	-20.0%	12.2%	0.744
Moderate	114	61	40.1%	26	14	28.0%	12.1%	-3.7%	27.8%	0.133
Severe	21	16	10.5%	5	5	10.0%	0.5%	-15.5%	16.5%	0.999
AE Resolution Status										
Resolved without Sequelae	145	76	50.0%	48	26	52.0%	-2.0%	-18.1%	14.2%	0.871
Resolved with Sequelae	9	8	5.3%	3	2	4.0%	1.3%	-14.9%	17.4%	0.999
Unresolved at Study Exit/Completion	87	55	36.2%	21	17	34.0%	2.2%	-13.5%	18.1%	0.865
Unknown	1	1	0.7%	0	0	0.0%	0.7%	-15.5%	16.8%	0.999
Other	2	2	1.3%	0	0	0.0%	1.3%	-14.8%	17.4%	0.999
Anticipated Events	100	66	43.4%	28	19	38.0%	5.4%	-10.6%	21.3%	0.515
Unanticipated Events	145	73	48.0%	44	27	54.0%	-6.0%	-22.0%	10.2%	0.516

Notes:
[1] Lower and upper bounds of exact 95% confidence interval for the group difference in percentages experiencing the event.
[2] Fisher's Exact Test

9.1 All Adverse Events

All adverse events, as shown in Table 16 below, are reported from the "Safety Population" which included 152 Cartiva patients and 50 Arthrodesis patients enrolled in the multi-center clinical study. Adverse event rates presented are based on the number of patients having at least one occurrence for a particular adverse event divided by the total number of patients in that treatment group.

A total of 105 Cartiva patients (69.1%) had at least one adverse event within 24 months versus 36 Arthrodesis patients (72.0%). A total of 245 events were reported in the Cartiva patients and 72 events were reported in the Arthrodesis patients. The summary of AEs by System Organ Class (SOC) and Preferred Term (PT) in either treatment group is provided in the Table below reported as number of events and number of patients in the safety population.

Table 16: All Adverse Events [CARTIVA Table]

All Adverse Events	All (N = 202)			Cartiva (N = 152)			Fusion (N = 50)		
	Events	Subjects	%	Events	Subjects	%	Events	Subjects	%
All Adverse Events	317	141	69.8%	245	105	69.1%	72	36	72.0%
BLOOD AND LYMPHATIC SYSTEM DISORDERS	1	1	0.5%	1	1	0.7%	0	0	0.0%
Splenomegaly	1	1	0.5%	1	1	0.7%	0	0	0.0%
CARDIAC DISORDERS	2	2	1.0%	2	2	1.3%	0	0	0.0%
Aortic valve stenosis	1	1	0.5%	1	1	0.7%	0	0	0.0%
Aortic valve disease	1	1	0.5%	1	1	0.7%	0	0	0.0%
CONGENITAL, FAMILIAL, AND GENETIC DISORDERS	1	1	0.5%	1	1	0.7%	0	0	0.0%
Congenital foot malformation	1	1	0.5%	1	1	0.7%	0	0	0.0%
EAR AND LABYRINTH DISORDERS	2	1	0.5%	2	1	0.7%	0	0	0.0%
Eustachian tube patulous	2	1	0.5%	2	1	0.7%	0	0	0.0%
ENDOCRINE DISORDERS	1	1	0.5%	1	1	0.7%	0	0	0.0%
Hypothyroidism	1	1	0.5%	1	1	0.7%	0	0	0.0%
GASTROINTESTINAL DISORDERS	7	7	3.5%	6	6	3.9%	1	1	2.0%
Abdominal pain upper	2	2	1.0%	2	2	1.3%	0	0	0.0%
Diverticulum	1	1	0.5%	1	1	0.7%	0	0	0.0%
Gastrointestinal pain	1	1	0.5%	1	1	0.7%	0	0	0.0%
Salivary gland calculus	1	1	0.5%	1	1	0.7%	0	0	0.0%
Small intestinal obstruction	1	1	0.5%	1	1	0.7%	0	0	0.0%
Tongue oedema	1	1	0.5%	0	0	0.0%	1	1	2.0%
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	30	25	12.4%	28	23	15.1%	2	2	4.0%
Fibrosis	1	1	0.5%	1	1	0.7%	0	0	0.0%
Gait disturbance	3	2	1.0%	3	2	1.3%	0	0	0.0%
Impaired healing	2	2	1.0%	1	1	0.7%	1	1	2.0%
Oedema peripheral	1	1	0.5%	1	1	0.7%	0	0	0.0%
Non-cardiac chest pain	1	1	0.5%	0	0	0.0%	1	1	2.0%
Implant site pain	18	16	7.9%	18	16	10.5%	0	0	0.0%
Implant site cyst	1	1	0.5%	1	1	0.7%	0	0	0.0%
Implant site induration	1	1	0.5%	1	1	0.7%	0	0	0.0%
Implant site swelling	2	2	1.0%	2	2	1.3%	0	0	0.0%
HEPATOBILIARY DISORDERS	3	3	1.5%	3	3	2.0%	0	0	0.0%
Cholecystitis	1	1	0.5%	1	1	0.7%	0	0	0.0%
Cholecystitis acute	1	1	0.5%	1	1	0.7%	0	0	0.0%

Hepatomegaly	1	1	0.5%	1	1	0.7%	0	0	0.0%
INFECTIONS AND INFESTATIONS	20	17	8.4%	13	12	7.9%	7	5	10.0%
Arthritis viral	1	1	0.5%	1	1	0.7%	0	0	0.0%
Bronchitis	1	1	0.5%	1	1	0.7%	0	0	0.0%
Clostridium difficile colitis	1	1	0.5%	1	1	0.7%	0	0	0.0%
Cystitis	1	1	0.5%	1	1	0.7%	0	0	0.0%
Herpes zoster	1	1	0.5%	1	1	0.7%	0	0	0.0%
Influenza	1	1	0.5%	1	1	0.7%	0	0	0.0%
Nasopharyngitis	2	2	1.0%	2	2	1.3%	0	0	0.0%
Onychomycosis	1	1	0.5%	0	0	0.0%	1	1	2.0%
Pneumonia	2	2	1.0%	1	1	0.7%	1	1	2.0%
Postoperative wound infection	1	1	0.5%	1	1	0.7%	0	0	0.0%
Sepsis	1	1	0.5%	0	0	0.0%	1	1	2.0%
Sinusitis	2	2	1.0%	1	1	0.7%	1	1	2.0%
Stitch abscess	1	1	0.5%	1	1	0.7%	0	0	0.0%
Urinary tract infection	4	3	1.5%	1	1	0.7%	3	2	4.0%
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	117	78	38.6%	86	57	37.5%	31	21	42.0%
Ankle fracture	2	2	1.0%	2	2	1.3%	0	0	0.0%
Back injury	1	1	0.5%	1	1	0.7%	0	0	0.0%
Device breakage	1	1	0.5%	0	0	0.0%	1	1	2.0%
Device migration	1	1	0.5%	1	1	0.7%	0	0	0.0%
Fall	1	1	0.5%	1	1	0.7%	0	0	0.0%
Foot fracture	7	6	3.0%	6	5	3.3%	1	1	2.0%
Hand fracture	1	1	0.5%	1	1	0.7%	0	0	0.0%
Humerus fracture	1	1	0.5%	1	1	0.7%	0	0	0.0%
Joint sprain	2	2	1.0%	2	2	1.3%	0	0	0.0%
Road traffic accident	1	1	0.5%	1	1	0.7%	0	0	0.0%
Spinal cord injury	1	1	0.5%	1	1	0.7%	0	0	0.0%
Tendon rupture	1	1	0.5%	1	1	0.7%	0	0	0.0%
Muscle strain	1	1	0.5%	1	1	0.7%	0	0	0.0%
Contusion	2	2	1.0%	1	1	0.7%	1	1	2.0%
Comminuted fracture	1	1	0.5%	1	1	0.7%	0	0	0.0%
Meniscus lesion	1	1	0.5%	1	1	0.7%	0	0	0.0%
Medical device complication	4	4	2.0%	0	0	0.0%	4	4	8.0%
Post procedural bile leak	1	1	0.5%	1	1	0.7%	0	0	0.0%
Post procedural discharge	1	1	0.5%	1	1	0.7%	0	0	0.0%
Post procedural complication	2	2	1.0%	1	1	0.7%	1	1	2.0%
Medical device pain	8	8	4.0%	6	6	3.9%	2	2	4.0%

Joint injury	7	5	2.5%	5	4	2.6%	2	1	2.0%
Limb injury	5	3	1.5%	2	1	0.7%	3	2	4.0%
Skeletal injury	2	1	0.5%	2	1	0.7%	0	0	0.0%
Postoperative wound complication	1	1	0.5%	0	0	0.0%	1	1	2.0%
Post procedural oedema	5	5	2.5%	3	3	2.0%	2	2	4.0%
Limb crushing injury	1	1	0.5%	0	0	0.0%	1	1	2.0%
Procedural pain	40	38	18.8%	31	29	19.1%	9	9	18.0%
Avulsion fracture	1	1	0.5%	1	1	0.7%	0	0	0.0%
Post procedural swelling	14	13	6.4%	11	10	6.6%	3	3	6.0%
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	88	62	30.7%	68	46	30.3%	20	16	32.0%
Arthralgia	19	18	8.9%	16	15	9.9%	3	3	6.0%
Arthritis	7	6	3.0%	4	4	2.6%	3	2	4.0%
Arthropathy	2	1	0.5%	2	1	0.7%	0	0	0.0%
Back pain	3	3	1.5%	1	1	0.7%	2	2	4.0%
Bone cyst	1	1	0.5%	1	1	0.7%	0	0	0.0%
Bunion	3	3	1.5%	2	2	1.3%	1	1	2.0%
Bursitis	1	1	0.5%	1	1	0.7%	0	0	0.0%
Cervical spinal stenosis	1	1	0.5%	0	0	0.0%	1	1	2.0%
Exostosis	1	1	0.5%	1	1	0.7%	0	0	0.0%
Fracture nonunion	2	2	1.0%	0	0	0.0%	2	2	4.0%
Joint stiffness	2	2	1.0%	2	2	1.3%	0	0	0.0%
Metatarsalgia	1	1	0.5%	0	0	0.0%	1	1	2.0%
Monarthritis	1	1	0.5%	1	1	0.7%	0	0	0.0%
Muscle spasms	1	1	0.5%	1	1	0.7%	0	0	0.0%
Musculoskeletal pain	1	1	0.5%	0	0	0.0%	1	1	2.0%
Osteoarthritis	8	5	2.5%	7	4	2.6%	1	1	2.0%
Pain in extremity	12	11	5.4%	11	10	6.6%	1	1	2.0%
Palindromic rheumatism	1	1	0.5%	1	1	0.7%	0	0	0.0%
Plantar fasciitis	3	3	1.5%	2	2	1.3%	1	1	2.0%
Spinal column stenosis	1	1	0.5%	1	1	0.7%	0	0	0.0%
Tendonitis	4	3	1.5%	3	2	1.3%	1	1	2.0%
Fibromyalgia	2	2	1.0%	2	2	1.3%	0	0	0.0%
Muscle tightness	1	1	0.5%	1	1	0.7%	0	0	0.0%
Joint crepitation	1	1	0.5%	1	1	0.7%	0	0	0.0%
Foot deformity	8	7	3.5%	7	6	3.9%	1	1	2.0%
Limb discomfort	1	1	0.5%	0	0	0.0%	1	1	2.0%
NEOPLASMS BENIGN, MALIGNANT, AND UNSPECIFIED	8	7	3.5%	6	5	3.3%	2	2	4.0%

(INCL CYSTS AND POLYPS)									
B-cell lymphoma	1	1	0.5%	1	1	0.7%	0	0	0.0%
Neuroma	1	1	0.5%	1	1	0.7%	0	0	0.0%
Throat cancer	1	1	0.5%	1	1	0.7%	0	0	0.0%
Gastrointestinal stromal tumour	1	1	0.5%	0	0	0.0%	1	1	2.0%
Prostate cancer	2	2	1.0%	2	2	1.3%	0	0	0.0%
Benign soft tissue neoplasm	1	1	0.5%	0	0	0.0%	1	1	2.0%
Benign muscle neoplasm	1	1	0.5%	1	1	0.7%	0	0	0.0%
NERVOUS SYSTEM DISORDERS	7	6	3.0%	5	5	3.3%	2	1	2.0%
Carpal tunnel syndrome	1	1	0.5%	1	1	0.7%	0	0	0.0%
Dysaesthesia	1	1	0.5%	0	0	0.0%	1	1	2.0%
Hypoaesthesia	1	1	0.5%	0	0	0.0%	1	1	2.0%
Neuralgia	1	1	0.5%	1	1	0.7%	0	0	0.0%
Neuropathy peripheral	1	1	0.5%	1	1	0.7%	0	0	0.0%
Syncope	1	1	0.5%	1	1	0.7%	0	0	0.0%
Cognitive disorder	1	1	0.5%	1	1	0.7%	0	0	0.0%
PREGNANCY, PUERPERIUM AND PERINATAL CONDITIONS	2	2	1.0%	1	1	0.7%	1	1	2.0%
Pregnancy	2	2	1.0%	1	1	0.7%	1	1	2.0%
PSYCHIATRIC DISORDERS	6	6	3.0%	5	5	3.3%	1	1	2.0%
Anxiety	2	2	1.0%	2	2	1.3%	0	0	0.0%
Depression	3	3	1.5%	2	2	1.3%	1	1	2.0%
Insomnia	1	1	0.5%	1	1	0.7%	0	0	0.0%
RENAL AND URINARY DISORDERS	1	1	0.5%	0	0	0.0%	1	1	2.0%
Nephrolithiasis	1	1	0.5%	0	0	0.0%	1	1	2.0%
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	2	2	1.0%	1	1	0.7%	1	1	2.0%
Metrorrhagia	1	1	0.5%	0	0	0.0%	1	1	2.0%
Postmenopausal haemorrhage	1	1	0.5%	1	1	0.7%	0	0	0.0%
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	4	3	1.5%	4	3	2.0%	0	0	0.0%
Dysphonia	1	1	0.5%	1	1	0.7%	0	0	0.0%
Dyspnoea	1	1	0.5%	1	1	0.7%	0	0	0.0%
Nasal septum deviation	1	1	0.5%	1	1	0.7%	0	0	0.0%
Sleep apnoea syndrome	1	1	0.5%	1	1	0.7%	0	0	0.0%
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	8	7	3.5%	6	5	3.3%	2	2	4.0%
Dyshidrosis	1	1	0.5%	1	1	0.7%	0	0	0.0%

Ingrowing nail	1	1	0.5%	1	1	0.7%	0	0	0.0%
Rash	2	2	1.0%	2	2	1.3%	0	0	0.0%
Scar	1	1	0.5%	1	1	0.7%	0	0	0.0%
Skin disorder	1	1	0.5%	0	0	0.0%	1	1	2.0%
Skin lesion	1	1	0.5%	1	1	0.7%	0	0	0.0%
Skin ulcer	1	1	0.5%	0	0	0.0%	1	1	2.0%
SURGICAL AND MEDICAL PROCEDURES	4	4	2.0%	3	3	2.0%	1	1	2.0%
Bunion operation	1	1	0.5%	1	1	0.7%	0	0	0.0%
Hip Arthroplasty	1	1	0.5%	1	1	0.7%	0	0	0.0%
Hysterectomy	1	1	0.5%	0	0	0.0%	1	1	2.0%
Muscle operation	1	1	0.5%	1	1	0.7%	0	0	0.0%
VASCULAR DISORDERS	3	3	1.5%	3	3	2.0%	0	0	0.0%
Hypertension	3	3	1.5%	3	3	2.0%	0	0	0.0%

From the table above, one can see that there are three categories of adverse events for Preferred Term in which the Cartiva group is greater than or equal to approximately four percentage points higher for number of subject experiencing these events than the Arthrodesis group. These PT categories include: Implant site pain (10.5% vs 0%); Arthralgia (9.9% vs 6.0%); and Pain in the Extremity (6.6% vs 2.0%). Specifically, a higher percentage of Cartiva subjects had adverse events involving pain. The correlation of subjects with high rates of pain measured as adverse events as it correlates with primary outcome measures for device effectiveness is unclear.

There were two PT categories where the number of subjects experiencing an adverse event was greater in the control group: Fracture Non-union (4.0% vs 0%) and Medical Device Complications (8.0% vs 0%), which also is defined as including non-union and delayed union for the Arthrodesis group. Fracture Non-union is not a clinically relevant comparison, as the investigational device does not intend union.

Among the SOC categories, there are a greater percentage of Cartiva subjects (15.1% vs 4.0%) who experienced "General Disorders and Administration Site Conditions". The PT categories under this SOC category shows that there are a greater percentage of Cartiva subject involved with Implant Site Pain (10.5% vs 0%), Gait Disturbance (1.3% vs 0 %), and Implant Site Swelling (1.3% vs 0%).

9.2 Treatment Emergent Adverse Events

The incidence of what the sponsor considered as Treatment-Emergent Adverse Events (TEAE) among subjects was similar between the groups (44% Cartiva and 42% Arthrodesis).

There were an overall total of 134 TEAEs reported within the safety population. A total of 102 events (76.1% of total events) in 67 subjects (44.1% of Cartiva subjects) were reported in the Cartiva patients and 32 events (23.8% of total events) in 21 subjects (42.0% of fusion subjects) were reported in the Arthrodesis group. Therefore, the numbers of subjects experiencing adverse events were similar

between groups. The summary of AEs by SOC and PT in either treatment group is provided in Table 17 below reported as number of events and number of patients in the safety population.

Table 17: All Treatment Emergent Events [CARTIVA Table]

Treatment Emergent	All (N = 202)			Cartiva (N = 152)			Fusion (N = 50)		
	Events	Subjects	%	Events	Subjects	%	Events	Subjects	%
All Treatment Emergent Events	134	88	43.6%	102	67	44.1%	32	21	42.0%
CONGENITAL, FAMILIAL, AND GENETIC DISORDERS	1	1	0.5%	1	1	0.7%	0	0	0.0%
Congenital foot malformation	1	1	0.5%	1	1	0.7%	0	0	0.0%
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	26	22	10.9%	25	21	13.8%	1	1	2.0%
Fibrosis	1	1	0.5%	1	1	0.7%	0	0	0.0%
Gait disturbance	1	1	0.5%	1	1	0.7%	0	0	0.0%
Impaired healing	2	2	1.0%	1	1	0.7%	1	1	2.0%
Implant site pain	18	16	7.9%	18	16	10.5%	0	0	0.0%
Implant site cyst	1	1	0.5%	1	1	0.7%	0	0	0.0%
Implant site induration	1	1	0.5%	1	1	0.7%	0	0	0.0%
Implant site swelling	2	2	1.0%	2	2	1.3%	0	0	0.0%
INFECTIONS AND INFESTATIONS	1	1	0.5%	1	1	0.7%	0	0	0.0%
Stitch abscess	1	1	0.5%	1	1	0.7%	0	0	0.0%
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	81	61	30.2%	57	43	28.3%	24	18	36.0%
Device breakage	1	1	0.5%	0	0	0.0%	1	1	2.0%
Device migration	1	1	0.5%	1	1	0.7%	0	0	0.0%
Foot fracture	3	3	1.5%	2	2	1.3%	1	1	2.0%
Comminuted fracture	1	1	0.5%	1	1	0.7%	0	0	0.0%
Medical device complication	4	4	2.0%	0	0	0.0%	4	4	8.0%
Post procedural discharge	1	1	0.5%	1	1	0.7%	0	0	0.0%
Post procedural complication	2	2	1.0%	1	1	0.7%	1	1	2.0%
Medical device pain	8	8	4.0%	6	6	3.9%	2	2	4.0%
Postoperative wound complication	1	1	0.5%	0	0	0.0%	1	1	2.0%
Post procedural oedema	5	5	2.5%	3	3	2.0%	2	2	4.0%
Procedural pain	40	38	18.8%	31	29	19.1%	9	9	18.0%
Post procedural swelling	14	13	6.4%	11	10	6.6%	3	3	6.0%
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	17	12	5.9%	14	9	5.9%	3	3	6.0%

Arthritis	1	1	0.5%	1	1	0.7%	0	0	0.0%
Arthropathy	2	1	0.5%	2	1	0.7%	0	0	0.0%
Bone cyst	1	1	0.5%	1	1	0.7%	0	0	0.0%
Bunion	1	1	0.5%	1	1	0.7%	0	0	0.0%
Exostosis	1	1	0.5%	1	1	0.7%	0	0	0.0%
Fracture nonunion	2	2	1.0%	0	0	0.0%	2	2	4.0%
Joint stiffness	2	2	1.0%	2	2	1.3%	0	0	0.0%
Tendonitis	3	2	1.0%	2	1	0.7%	1	1	2.0%
Foot deformity	4	3	1.5%	4	3	2.0%	0	0	0.0%
NERVOUS SYSTEM DISORDERS	4	3	1.5%	2	2	1.3%	2	1	2.0%
Dysaesthesia	1	1	0.5%	0	0	0.0%	1	1	2.0%
Hypoaesthesia	1	1	0.5%	0	0	0.0%	1	1	2.0%
Neuralgia	1	1	0.5%	1	1	0.7%	0	0	0.0%
Neuropathy peripheral	1	1	0.5%	1	1	0.7%	0	0	0.0%
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	3	3	1.5%	1	1	0.7%	2	2	4.0%
Scar	1	1	0.5%	1	1	0.7%	0	0	0.0%
Skin disorder	1	1	0.5%	0	0	0.0%	1	1	2.0%
Skin ulcer	1	1	0.5%	0	0	0.0%	1	1	2.0%
SURGICAL AND MEDICAL PROCEDURES	1	0	0.0%	1	0	0.0%	0	0	0.0%
Bunion operation	1	1	0.5%	1	1	0.7%	0	0	0.0%

Similar to the All Adverse Events table, in the TEAE table there is one category (Implant Site Pain) in which the Cartiva group is greater than four percentage points higher for the number of subjects experiencing these events than those in the Arthrodesis group. This PT category is Implant Site Pain (10.5% vs 0%). Specifically, a higher percentage of Cartiva subjects had treatment emergent adverse events considered as serious involving pain. As stated previously, the correlation of subjects with high rates of pain measured as serious adverse events as it correlates with primary outcome measures for device effectiveness is unclear.

Again similar to the All Adverse Events table, there were two PT categories where the number of subjects experiencing a TEAE was greater in the control group: Fracture Non-union (4.0% vs 0%) and Medical Device Complications (8.0% vs 0%), which also is defined as including non-union and delayed union for the Arthrodesis group. Fracture Non-union is not a clinically relevant comparison, as the investigational device does not intend union.

For the SOC category, there are a greater percentage of Cartiva subjects (13.8% vs 2.0%) who experienced "General Disorders and Administration Site Conditions" TEAEs**.** The PT categories under this SOC category shows that there are a greater percentage of Cartiva subject involved with Implant Site Pain (10.5% vs 0%), and Implant Site Swelling (1.3% vs 0%).

For the SOC category "Infections and Infestations", there were a greater percentage of Cartiva subjects (0.7% vs 0%) compared to Arthrodesis. This specifically includes the PT category of Stitch Abscess, with one Cartiva patient involved.

Serious Adverse Events (SAEs) are usually defined as World Health Organization (WHO) Grade 3 or 4. There were a total of 26 serious adverse events (SAE) noted by FDA on their review of the "Safety" population in the original PMA data. Upon a deficiency request, FDA asked that serious adverse events be categorized by the WHO classification. The sponsor reports 11 SAEs according to WHO classification as show in their table below.

Table 18: Sponsor's SAEs according to WHO classification [CARTIVA Table]

Treatment Group	Preferred Term	Relationship	Severity	WHO Grade
ROLLIN	Ankle fracture	SYSTEMIC (NON-DEVICE) RELATED	SEVERE	3
ROLLIN	Implant site pain	DEVICE RELATED	SEVERE	3
ROLLIN	Postoperative pain	OPERATIVE SITE RELATED	SEVERE	3
C	Prostate cancer	SYSTEMIC (NON-DEVICE) RELATED	SEVERE	3
C	Arthritis	SYSTEMIC (NON-DEVICE) RELATED	SEVERE	3
C	Small intestinal obstruction	SYSTEMIC (NON-DEVICE) RELATED	SEVERE	3
C	Cholecystitis acute	SYSTEMIC (NON-DEVICE) RELATED	SEVERE	3
C	Medical device pain	DEVICE RELATED	SEVERE	3
C	Implant site pain	DEVICE RELATED	SEVERE	3
C	Implant site pain	DEVICE RELATED	SEVERE	3
C	Hip arthroplasty	SYSTEMIC (NON-DEVICE) RELATED	SEVERE	3

9.3 All Device-Related Adverse Events

The sponsor reports device related adverse events as a subgroup of Treatment Emergent Adverse Events. There were 35 total events that were analyzed. These are outlined in Table 19 below.

Table 19: All Device Related Events [CARTIVA Table]

Device Related	All (N = 202)			Cartiva (N = 152)			Fusion (N = 50)		
	Events	Subjects	%	Events	Subjects	%	Events	Subjects	%
All Device Related Events	35	27	13.4%	31	23	15.1%	4	4	8.0%
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	22	18	8.9%	22	18	11.8%	0	0	0.0%
Implant site pain	18	16	7.9%	18	16	10.5%	0	0	0.0%
Implant site cyst	1	1	0.5%	1	1	0.7%	0	0	0.0%
Implant site induration	1	1	0.5%	1	1	0.7%	0	0	0.0%
Implant site swelling	2	2	1.0%	2	2	1.3%	0	0	0.0%
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	11	11	5.4%	7	7	4.6%	4	4	8.0%
Device breakage	1	1	0.5%	0	0	0.0%	1	1	2.0%
Device migration	1	1	0.5%	1	1	0.7%	0	0	0.0%
Medical device complication	1	1	0.5%	0	0	0.0%	1	1	2.0%
Medical device pain	8	8	4.0%	6	6	3.9%	2	2	4.0%
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	2	2	1.0%	2	2	1.3%	0	0	0.0%
Joint stiffness	1	1	0.5%	1	1	0.7%	0	0	0.0%
Tendonitis	1	1	0.5%	1	1	0.7%	0	0	0.0%

9.4 Device Related Complications

From the analysis, there was 7% greater number of Cartiva patients who experienced device related events than control patients (15.1% Cartiva vs 8% Arthrodesis). The majority of these were attributed to device pain (Implant Site Pain 10.5% vs 0%). Implant site pain by PT as a TEAE was 10% greater in the Cartiva group than in the control group.

9.4.1 Serious Device-Related Adverse Events

As shown in the table above, there were 31 Cartiva patients and 4 Arthrodesis patients who had adverse events classified as device-related complications over 24 months. Table 20 below outlines those serious adverse events further considered by the sponsor as device related. Again the majority of these serious device related adverse event are attributed to the Cartiva device under the PT of Implant Site Pain (5.3% vs 0%)

Table 20: All Device Related Serious Adverse Events [CARTIVA Table]

Device Related Serious Adverse Events	All (N = 202)			Cartiva (N = 152)			Fusion (N = 50)		
	Events	Subjects	%	Events	Subjects	%	Events	Subjects	%
All Device Related Serious Adverse Events	13	13	6.4%	11	11	7.2%	2	2	4.0%
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	8	8	4.0%	8	8	5.3%	0	0	0.0%
Implant site pain	8	8	4.0%	8	8	5.3%	0	0	0.0%
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	5	5	2.5%	3	3	2.0%	2	2	4.0%
Medical device complication	1	1	0.5%	0	0	0.0%	1	1	2.0%
Medical device pain	4	4	2.0%	3	3	2.0%	1	1	2.0%

In the table these events are further categorized by severity. The table below depicts serious device related adverse events by severity. The percentage of the total safety population is considered. Again, Implant Site Pain, Implant Site Swelling, and Medical Device Pain are considered as moderate to severe serious adverse events greater in the Cartiva subjects.

Table 21: Severity Events [CARTIVA Table]

Cartiva Patients	Mild		Moderate		Severe		Total	
	n	%	n	%	n	%	n	%
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	10	5	9	4.5	3	1.5	22	1.0
Implant site pain	7	3.5	8	4	3	1.5	18	8.9
Implant site cyst	1	0.05	0	0	0	0	1	0.05
Implant site induration	0	0	1	0.05	0	0	1	0.05
Implant site swelling	2	1	0	0	0	0	2	1
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	1	0.05	5	2.5	1	0.05	7	3.5
Device migration1	0	0	1	0.05	0	0	1	0.05
Medical device pain	1	0.05	4	2	1	0.05	6	3
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	2	1	0	0	0	0	2	1
Joint stiffness	1	0.05	0	0	0	0	1	0.05
Tendonitis	1	0.05	0	0	0	0	1	0.05

Arthrodesis Patients	Mild	Moderate	Severe	Total

	n	%	n	%	n	%	n	%
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	0	0.0%	3	75.0%	1	25.0%	4	100.0%
Device breakage	0	0	1	0.05%	0	0	1	0.05
Medical device complication	0	0	0	0	1	0.05	1	0.05
Medical device pain	0	0	2	1	0	0	2	1

From listings of Device Related and Operative Site Related adverse events in the original PMA, it appears that the sponsor did provide a complete analysis of all of the events listed. These were further determined by the Medical Monitor as being associated with the surgery, study device, or reduction, fixation or immobilization. FDA has communicated to the sponsor that some device complications potentially were misclassified as non-serious device-related adverse events.

9.4.2 Procedure-Associated Adverse Events

Operative site related events were those AEs that were associated with the surgery, a subset of the TEAE dataset. There were 99 total events that were analyzed. From the sponsor's analysis, there were a similar percentage of Cartiva patients who experienced operative site related events compared to that experienced by control patients (33.6% Cartiva vs 36% Arthrodesis).

An overall summary of all complications associated with surgical procedures is presented in Table 22 below. Procedure associated adverse events were reported for 33.6% of Cartiva patients compared to 36.0% of controls.

Table 22: Procedure Related Adverse Events [CARTIVA Table]

Procedure Related Adverse Events	All (N = 202)			Cartiva (N = 152)			Fusion (N = 50)		
	Events	Subjects	%	Events	Subjects	%	Events	Subjects	%
All Procedure Related Adverse Events	99	69	34.2 %	71	51	33.6 %	28	18	36.0 %
CONGENITAL, FAMILIAL, AND GENETIC DISORDERS	1	1	0.5%	1	1	0.7%	0	0	0.0%
Congenital foot malformation	1	1	0.5%	1	1	0.7%	0	0	0.0%
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	4	4	2.0%	3	3	2.0%	1	1	2.0%
Fibrosis	1	1	0.5%	1	1	0.7%	0	0	0.0%
Gait disturbance	1	1	0.5%	1	1	0.7%	0	0	0.0%
Impaired healing	2	2	1.0%	1	1	0.7%	1	1	2.0%
INFECTIONS AND INFESTATIONS	1	1	0.5%	1	1	0.7%	0	0	0.0%

Stitch abscess	1	1	0.5%	1	1	0.7%	0	0	0.0%
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	70	52	25.7 %	50	37	24.3 %	20	15	30.0 %
Foot fracture	3	3	1.5%	2	2	1.3%	1	1	2.0%
Comminuted fracture	1	1	0.5%	1	1	0.7%	0	0	0.0%
Medical device complication	3	3	1.5%	0	0	0.0%	3	3	6.0%
Post procedural discharge	1	1	0.5%	1	1	0.7%	0	0	0.0%
Post procedural complication	2	2	1.0%	1	1	0.7%	1	1	2.0%
Postoperative wound complication	1	1	0.5%	0	0	0.0%	1	1	2.0%
Post procedural oedema	5	4	2.0%	3	2	1.3%	2	2	4.0%
Procedural pain	40	32	15.8 %	31	26	17.1 %	9	6	12.0 %
Post procedural swelling	14	5	2.5%	11	4	2.6%	3	1	2.0%
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	15	7	3.5%	12	7	4.6%	3	0	0.0%
Arthritis	1	0	0.0%	1	0	0.0%	0	0	0.0%
Arthropathy	2	1	0.5%	2	1	0.7%	0	0	0.0%
Bone cyst	1	1	0.5%	1	1	0.7%	0	0	0.0%
Bunion	1	1	0.5%	1	1	0.7%	0	0	0.0%
Exostosis	1	1	0.5%	1	1	0.7%	0	0	0.0%
Fracture nonunion	2	0	0.0%	0	0	0.0%	2	0	0.0%
Joint stiffness	1	1	0.5%	1	1	0.7%	0	0	0.0%
Tendonitis	2	1	0.5%	1	1	0.7%	1	0	0.0%
Foot deformity	4	1	0.5%	4	1	0.7%	0	0	0.0%
NERVOUS SYSTEM DISORDERS	4	2	1.0%	2	2	1.3%	2	0	0.0%
Dysaesthesia	1	0	0.0%	0	0	0.0%	1	0	0.0%
Hypoaesthesia	1	0	0.0%	0	0	0.0%	1	0	0.0%
Neuralgia	1	1	0.5%	1	1	0.7%	0	0	0.0%
Neuropathy peripheral	1	1	0.5%	1	1	0.7%	0	0	0.0%
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	3	2	1.0%	1	0	0.0%	2	2	4.0%
Scar	1	0	0.0%	1	0	0.0%	0	0	0.0%
Skin disorder	1	1	0.5%	0	0	0.0%	1	1	2.0%
Skin ulcer	1	1	0.5%	0	0	0.0%	1	1	2.0%
SURGICAL AND MEDICAL PROCEDURES	1	0	0.0%	1	0	0.0%	0	0	0.0%
Bunion operation	1	0	0.0%	1	0	0.0%	0	0	0.0%

9.5 Subsequent Secondary Surgical Interventions (SSSI)

Secondary surgical procedures were termed as "Subsequent Secondary Surgical Interventions" (SSSI) by the sponsor. Secondary surgical procedures were documented to include revisions, removals, reoperation, and/or supplemental fixations over 24 months. The definitions for SSSIs were applied as outlined in the FDA's Guidance document, "Guidance for Industry and FDA Staff: Clinical Data Presentations for Orthopedic Device Applications".

SSSIs were determined as to whether or not, for example, a secondary surgical procedure was required to treat non-unions and to remove broken hardware in fusion subjects and to address mechanical failure, device fracture, or device dislodgement in Cartiva subjects. The major complications associated with Cartiva and listed as part of the sponsor's Risk Analysis included implant fracture or dislocation, any additional surgical interventions for the purpose of addressing development of osteonecrosis caused by the implant, and conversion to arthrodesis or any other implant revision surgical procedure.

From the sponsor's analysis, there were a total of 23 (23/202; 11%) of subjects who underwent a SSSI, with a similar incidence between groups (11% Cartiva and 12% Arthrodesis). A total of 14 (9.2%) Cartiva subjects and 4 (8%) arthrodesis subjects had the implant and/or hardware removed during the course of the study. A total of 17 Cartiva patients and 6 Fusion patients had an SSSI defined by the sponsor.

Table 23: SSSI [FDA Table]

SSSI	Cartiva® Roll-In (n=22)	Cartiva® Randomized (n=130)	Cartiva® Total (n=152)	Fusion (n=50)
Removal	4 (18.2%)	10 (7.7%)	14 (9.2%)	4 (8%)
Reoperation	0	1 (0.8%)	1 (0.7%)	0
Revision	0	1 (0.8%)	1 (0.7%)	3 (6%)
Supplemental Fixation	0	1 (0.8%)	1 (0.7%)	0
Overall	**4 (18.2%)**	**13 (10.0%)**	**17 (11.2%)**	**6[1] (12.0%)**

[1]One Fusion subject (02-031) experienced two events (one removal and one revision).

9.6 Radiographic Data

In addition to the other parameters discussed above, a safety assessment was determined at 24 months by an independent review of plain radiographs. Plain radiographs allow the assessment of abnormal bone formation at the fusion site in Arthrodesis subjects and loss of implant integrity with the Cartiva device. Qualitative evaluations included heterotopic ossification (HO), radiolucency, bony fractures, avascular necrosis (AVN), adverse bony reactions, device displacement, fusion status, device integrity, and additional observations.

In Table 24 below is a summation of the data as evaluated in both the safety population and the mITT population for Cartiva subjects. Please refer to Section 10.2.4 "Radiographic Endpoints" for a detailed discussion of the radiographic findings in the context of assessment of the composite primary endpoint.

Table 24: Radiographic Findings [CARTIVA Table]

Radiographic Finding	Cartiva® SCI Randomized (n=130)		Cartiva® SCI Safety (n=152)		Arthrodesis (n=50)	
	n	%	n	%	n	%
Radiographic Failure Modalities in Primary Endpoint						
Avascular Necrosis	0	0.0%	0	0.0%	0	0.0%
Device Displacement	0	0.0%	0	0.0%	--	--
Device Fragmentation	0	0.0%	0	0.0%	--	--
Non Union	--	--	--	--	4	8.0%
Mal Union	--	--	--	--	0	0.0%
Fractured Hardware	--	--	--	--	1	2.0%
Other Radiographic Findings						
Fusion (Cartiva® cohort)	0	0.0%	0	0.0%	--	--
Radiolucency (any)	5	3.8%	6	3.9%	6	12.0%
Bony Fracture	1	0.8%	1	0.7%	1	2.0%
Bony Reaction	64	49.2%	75	49.3%	3	6.0%
Heterotopic Ossification	75	57.7%	89	58.6%	24	48.0%

Radiographic Finding	Cartiva® SCI Randomized (n=130)		Cartiva® SCI Safety (n=152)		Arthrodesis (n=50)	
	n	%	n	%	n	%
Bony Reaction Only	25	19.2%	28	18.4%	1	2.0%
Heterotopic Ossification Only	36	27.7%	42	27.6%	22	44.0%
Bony Reaction + Heterotopic Ossification	39	30.0%	47	30.9%	2	4.0%
Any Bony Reaction or Heterotopic Ossification	100	76.9%	117	77.0%	25	50.0%
No Bony Reaction or Heterotopic Ossification	30	23.1%	35	23.0%	25	50.0%

Bony reactions were noted upon radiographic review, and analyses comparing outcomes in subjects with and without these bony reactions were conducted by the sponsor. The sponsor concluded that these radiographic findings had no clinical impact. (The classification criteria and the adjudication of the data were conducted by the Medical Monitor.) From the Agency's perspective, the clinical significance of the observed bony reactions remains unclear.

9.7 Safety Evaluation Summary

A safety summary is provided in both narrative and table forms for the "safety population" (202 treated subjects) out to 24 months. The sponsor subdivides adverse events collected from this population into 6 subgroups. Analyses of adverse events were not considered as part of the primary endpoint, unless they led to a SSSI. Adverse events are provided as a separate assessment of safety alone.

Table 25 below presents a summary of the adverse events analyzed at 24 Months as subgroups defined by the sponsor.

Table 25: Summary of Adverse Events at 24 Months as Subgroups Defined by Sponsor [FDA Table]

Event	Cartiva Mean (Min, Max) Events	Arthrodesis Mean (Min, Max) Events
Any Event	106/152 (69.74) (61.77, 76.92) 245	37/50 (74.00) (59.66, 85.37) 73
Non Treatment Emergent Events	67/152 (44.08) (36.04, 52.35) 103	21/50 (42.00) (28.19, 56.79) 32
Serious Adverse Events	30/152 (19.74) (13.73, 26.96) 36	10/50 (20.00) (10.03, 33.72) 13
Severity of Events Mild Moderate Severe	111/245 (45.31) (38.96, 51.77) 114/245(46.53) (40.16, 52.99) 20/245 (8.16) (5.06, 12.33)	41/73 (56.16) (44.05, 67.76) 27/73 (36.99) (25.97, 49.09) 5/73 (6.85) (2.26, 15.26)
Resolved Event Status Resolved without Seq Resolved with Seq Unresolved Unknown Other	 145/2442 (59.43) (52.98, 65.64) 10/244 (4.10) (1.98, 7.41) 86/244 (35.25) (29.26, 41.60) 1/244 (0.41) (0.01, 2.26) 2/244 (0.82) (0.10, 2.93)	 48/73 (65.75) (53.72, 76.47) 3/73 (4.11) (0.86, 11.54) 22/73 (30.14) (19.94, 42.00) 0/73 (0.00) (0.00, 4.93) 0/73 (0.00) (0.00, 4.93)
Unanticipated Events	144/245 (58.78) (52.33, 65.00)	45/73 (65.00) (53.52, 75.33)

[1]Lower and upper exact 95% confidence limits on the percentage.
[2]One Cartiva patient did not have a resolution status reported.

A total of 105 Cartiva patients had at least one adverse event within 24 months versus 36 Arthrodesis patients. A total of 245 events were reported in the Cartiva patients and 72 events were reported in the Arthrodesis patients. The numbers of subjects experiencing adverse events were similar between groups.

A higher percentage of Cartiva subjects had treatment emergent adverse events involving Implant Site pain (10.5% vs 0%). The correlation of subjects with high rates of pain measured as serious adverse events as it correlates with primary outcome measures for device effectiveness is unclear.

There were a greater percentage of Adverse events (>5%) that resolved without sequel in the Arthrodesis group (65.75%) than in the Cartiva group (59.43%). In addition, there were a greater percentage of Unanticipated Events (>6%) in the Arthrodesis group (65.0%) than in the Cartiva group (58.78%).

In summary, the primary safety concerns are the serious adverse events, secondary surgical intervention, and radiographic findings in patients treated with the Cartiva device when compared to the control group.

10. EFFECTIVENESS EVALUATION

10.1. Primary Effectiveness Endpoint

The pre-defined primary effectiveness endpoint of the trial was specified as improvements in pain and functional Foot and Ankle Ability (FAAM) sports subscale score at 12 months in the intent to treat population (ITT) using last observation carried forward (LOCF) for missing data. However, as mentioned in the statistical section, there were interactive discussions with the sponsor that resulted in several different analyses being conducted related to the primary effective endpoint.

In the following sections, assessments of the clinical success or failure of each individual are presented along with a determination as to how these assessments impact the number of subjects considered for each analysis population, as well as the ultimate impact on assessment of the primary effectiveness endpoint. Discussions are also provided regarding the problems encountered when interpreting the validity of the outcome instruments with the manner in which they are used.

Table 26 below shows the primary endpoint for all of the completers in the mITT population. This is followed by the pre-specified primary endpoint for all of those that reached 1 year in the mITT population. The next two rows show the primary endpoint with the 4 subjects that did not complete the study as successes and as failures. While it seems more reasonable, based on the evidence presented in the missing data section, to consider the missing subjects as successes, these two analyses provide a range of possible outcomes. The final row shows the primary per protocol analyses incorporating FDA's definition of major protocol violations.

Table 26: Primary analyses [FDA Table]

Analysis Group	Cartiva	Arthrodesis	Lower Bound of one-sided 95% Confidence Interval
Primary - Completers	103/129 (79.8%)	37/47 (78.7%)	-10.3%
Pre-Specified Primary - Completers	102/128 (79.7%)	38/47 (80.9%)	-12.3%

Primary - mITT Missing as Success	104/130 (80%)	40/50 (80%)	-10.9%
Primary – mITT Missing as Failure	103/130 (79.2%)	37/50 (74%)	-6.5%
Primary - Pre-Specified Per Protocol – Sponsor	98/122 (80.3%)	37/46 (80.4%)	-11.4%
Primary - Per Protocol FDA	86/107 (80.4%)	33/41 (80.5%)	-12.1%

The changes to the effectiveness component of the primary endpoint (i.e. from 12 months to 24 months) are seen to be favorable to the Cartiva implant. When the sponsor's pre-specified 15% non-inferiority margin is utilized, the study meets both its pre-specified primary composite endpoint (effectiveness assessed at 12 months) and the post-hoc assessment requested by FDA for the primary composite endpoint (effectiveness assessed at 24 months). However, as was discussed in section 7.1.7, FDA questions whether the 15% non-inferiority margin is clinically appropriate. If, for example, a lower non-inferiority margin of 10%, corresponding to that typically utilized in non-inferiority studies for other orthopedic implants, were to be utilized for the evaluation, then both the pre-specified and post-hoc primary composite endpoints would not be met for this study. Whatever non-inferiority margin is utilized, FDA believes this margin should correspond to a maximum clinically insignificant difference for the investigative and control treatments.

The non-inferiority margin therefore represents a level of evidence, and the confidence interval incorporates a statistical measure of certainty used in estimates. The Panel will be asked if the sponsor has provided the appropriate level of evidence to provide reasonable certainty that the investigational device is no worse than the control. Please refer to the Panel question presented in Section 7.1.7 Primary Effectiveness Endpoint and Study Success.

10.2 Parts of the Composite Endpoint

The composite endpoint shows similar results between Cartiva and arthrodesis, with both groups around 80% success in most analyses; however, it is dependent on the success criteria used for each group. The composite endpoint is one way of summarizing four separate endpoints, giving specific cutoffs to determine success and failure. It would be incorrect to say that because the two groups showed similar response rates for their composite endpoint that subjects in each group had similar results for each of the four components of the composite endpoint for each group. The next four sections will examine the components of the composite endpoint separately.

10.2.1 Pain – VAS

Visual Analog Scale (VAS) scores were used to evaluate pain at the operative site. Questionnaires asked the average amount of pain the subject had felt over the last week and were completed prior to treatment, and at 2 and 6 weeks, and 3, 6, 12, and 24 months, post-operatively.

For the analysis as originally defined, for overall site pain at month 12, the Cartiva patients reported a mean overall site pain assessment of 17.8 mm (mean improvement of 50.2 from baseline), compared with a mean pain assessment of 5.7 mm (mean improvement 63.6) in the Arthrodesis patients. These

results demonstrated statistical significance for analyses of variance for all assessments ($p<0.05$) except baseline and Week 2. The mean Arthrodesis VAS is >30% less than the mean Cartiva VAS at these same time points. A summation of the VAS pain (at the operative site) results analyzed up to 2 years is provided in Table 27 below.

Table 27: VAS Pain Over Time - Completed Cases Without Secondary Surgery [CARTIVA Table]

	Cartiva® Total Score						Fusion Total Score						t-test	Wilcoxon	Effect
	N	Mean	SD	Med	Min	Max	N	Mean	SD	Med	Min	Max	p-value[1]	p-value[2]	Size[3]
Baseline	130	68.0	13.9	68.3	27.8	100.0	50	69.3	14.3	70.0	38.0	97.5	0.571	0.529	-0.10
Week 2	130	38.5	28.7	29.5	0.0	99.9	49	39.2	23.8	40.5	0.0	96.5	0.874	0.572	-0.03
Week 6	128	33.2	24.7	27.4	0.0	96.0	48	17.2	17.6	10.6	0.0	64.5	<.0001	0.000	0.70
Month 3	128	29.4	23.2	23.8	0.0	88.0	46	15.5	13.1	12.0	0.0	56.8	0.000	0.000	0.67
Month 6	124	28.9	27.5	20.5	0.0	97.0	43	11.7	18.3	4.0	0.0	74.8	0.000	0.000	0.68
Month 12	123	17.8	23.0	9.0	0.0	91.0	43	5.7	8.5	2.3	0.0	30.8	0.001	0.000	0.60
Month 24	116	14.5	22.1	5.0	0.0	94.0	41	5.9	12.1	1.5	0.0	70.0	0.020	0.005	0.43

Notes:
[1] Two sample pooled t-test p-value
[2] Two sample Wilcoxon rank sum test p-value
[3] Standardized effect size (group difference in means divided by pooled within group SD).

Similarly, if one looks at VAS change from baseline, it can be seen that Arthrodesis subjects had significantly less pain at every time point from 6 weeks to 2 years. The difference between Cartiva and Arthrodesis in the level of pain reduction at the operative site was over 15 mm from 6 weeks to 6 months and was 12.9 mm at 1 year and 9.6 mm at 2 years.

Table 28: VAS Pain Change from Baseline - Completed Cases Without Secondary Surgery [CARTIVA Table]

	Cartiva® Total Score						Fusion Total Score						t-test	Wilcoxon	Effect
	N	Mean	SD	Med	Min	Max	N	Mean	SD	Med	Min	Max	p-value[1]	p-value[2]	Size[3]
Week 2	130	-29.5	31.0	-34.6	-92.5	32.5	49	-30.3	26.6	-34.0	-82.5	28.5	0.866	0.990	0.03
Week 6	128	-35.0	28.8	-39.5	-97.5	36.8	48	-52.3	21.7	-56.0	-97.0	13.3	0.000	0.000	0.64
Month 3	128	-38.6	27.4	-41.0	-87.0	24.3	46	-54.1	19.1	-59.0	-85.8	17.8	0.001	0.000	0.61
Month 6	124	-39.0	29.4	-44.9	-93.5	45.0	43	-57.6	23.6	-63.8	-95.0	29.0	0.000	0.000	0.67
Month 12	123	-50.3	24.4	-54.5	-94.3	13.0	43	-63.2	17.7	-66.3	-97.0	-18.0	0.002	0.002	0.57
Month 24	116	-53.2	24.4	-57.1	-93.0	21.0	41	-62.8	22.7	-68.0	-96.0	31.0	0.028	0.008	0.41

Notes:
[1] Two sample pooled t-test p-value
[2] Two sample Wilcoxon rank sum test p-value
[3] Standardized effect size (group difference in means divided by pooled within group SD).

To be considered a success in terms of pain at the operative site for the primary endpoint, a subject must demonstrate improvement (decrease) from baseline in VAS Pain of ≥30% at 12 months (pre-specified primary endpoint) or 24 months (requested post-hoc primary endpoint).

As shown above and in other analyses below, the Cartiva group has clinically significantly more mean pain at the operative site over time than the control group, though the pain reduction from baseline for the Cartiva group are within what is considered as a clinically meaningful reduction. The Arthrodesis group maintained overall lower pain scores at each follow-up visit and had a greater mean reduction in pain.

To be considered a success in terms of pain at the operative site, a subject must demonstrate improvement (decrease) from baseline in VAS Pain of ≥30% at 12 months (pre-specified primary endpoint) or 24 months (requested post-hoc primary endpoint analysis). It can be seen in the responder analysis below that the Arthrodesis group performed substantially better from 6 weeks to 2 years.

Table 29: VAS Responder Analysis for Pain Over Time – All Completed [FDA Table]

Time Point	Cartiva	Arthrodesis	Difference (C-A)	Superiority of Arth. p-value	Non-inferiority Conf. Int. L.B.
2 weeks	84/130 (65%)	32/49 (65%)	0	1.0	-13.8%
6 weeks	90/129 (70%)	44/48 (92%)	-12%	0.003	-31.2%
3 months	102/130 (78%)	46/48 (96%)	-18%	0.006	-25.0%
6 months	91/126 (72%)	44/46 (96%)	-14%	0.0006	-31.6%
1 year	115/130 (88%)	47/47 (100%)	-12%	0.012	-16.1%
2 years	114/128 (89%)	46/47 (98%)	-9%	0.073	-14.5%

In examining the responder analysis, the Arthrodesis group performed substantially better from 6 weeks to 1 year, the pre-specified primary endpoint, as well as at 2 years, the requested post-hoc primary endpoint. Please note that, under the sponsor's pre-specified hierarchical testing plan for secondary endpoints, statistical superiority for the Cartiva treatment group was not demonstrated for the first analyzed secondary endpoint of mean differences from baseline of VAS pain scores. Accordingly, the p-values should be interpreted with caution in Table 29 above and in any subsequent tables summarizing secondary endpoint analyses.

There are many potential ways to categorize change in pain. Instead of looking at a 30% reduction in pain, some consider a 20 point reduction in pain to be the Minimal Clinically Important Difference (MCID). The tables categorize change in VAS according to these cutoffs. Those subjects that saw a 30% reduction in pain often, but not always, saw a 20 point reduction in pain.

Table 30: VAS categories at 12 months [FDA Table, Post-Hoc Analysis]

	Cartiva n=130	Arthrodesis n=47
(≥ 20 points improvement)	114 (88%)	45 (96%)
(11-19 points improvement	4 (3%)	2 (4%)
(≤ 10 points improvement and ≤ 10 points worsening)	10 (8%)	0 (0%)
(≥ 10 points worsening)	2 (2%)	0 (0%)

Table 31: VAS categories at 24 months [FDA Table, Post-Hoc Analysis]

	Cartiva n=128	Arthrodesis n=47
(≥ 20 points improvement)	113 (88%)	45 (96%)
(11-19 points improvement	8 (6%)	1 (2%)
(≤ 10 points improvement and ≤ 10 points worsening)	4 (3%)	0 (0%)
(≥ 10 points worsening)	3 (2%)	1 (2%)

One limitation with determining success and failure based on a percent reduction in pain or a 20 point reduction in pain is that, depending on the baseline level of pain, one can still be in considerable pain and be counted as a success. For example, subject (b) (4) who had a baseline VAS of 90, was considered a study success even though she had a 24 month VAS of 60. This clearly represents an improvement, yet this subject clearly continued to experience significant pain.

The inclusion criteria required that subjects have a baseline VAS of at least 40, although 4 subjects were enrolled into the study with baseline scores below 40, including one subject with a baseline score as low as 28. There were 6 Cartiva subjects that were considered successes in terms of pain that had 24 month VAS scores over 30 (3 above 40). If these 6 subjects with high 24 month VAS scores were considered failures, then Cartiva would not be able to demonstrate non-inferiority at the 15% level.

Table 32: Primary Endpoint Sensitivity Analysis Where Subjects With 24 Month VAS>30 Are Considered Failures [FDA Table, Post-Hoc Analysis]

Analysis Group	Cartiva	Arthrodesis	Lower Bound of one-sided 95% Confidence Interval
Primary - Completers	97/129 (75.2%)	37/47 (78.7%)	-15.2%

Question for Panel: Cartiva subjects experienced significantly more pain at the pre-specified primary endpoint of 1 year. According to most measures Cartiva subjects experienced substantially more pain at every endpoint from 6 weeks to 2 years, at the requested post-hoc primary endpoint. Can Cartiva be considered non-inferior in terms of pain?

10.2.2 Function – FAAM

The pre-specified primary endpoint required maintenance of function from baseline in FAAM Sports score at 12 months (inclusive of a decrease <9). The updated primary endpoint required maintenance of function from baseline in FAAM ADL score at 24 months (inclusive of a decrease ≤ 8).

10.2.2.1 FAAM-Sports

FAAM Sports scores were used to evaluate each subject's improvement in sports participation. Subjects rate their current level of function during sports related activities from 0 to 100. There are eight components: Running, Jumping, Landing, Starting, and Stopping Quickly, Cutting/lateral movements,

Low impact activities, Ability to perform activity with your normal technique, and Ability to participate in a desired sport as long as the patient wished.

Questionnaires were completed prior to treatment, and at 2 and 6 weeks, and 3, 6, 12, and 24 months, post-operatively. Success in each category was defined as maintenance or improvement in status postoperatively as compared to the pre-operative condition.

The sponsor reported clinically significant functional success in sports activities with the device through the primary measure of FAAM Sports at 12 months. For overall Sports function, at month 12, the Cartiva patients reported a mean overall functional assessment score of 75.8 (mean improvement of 36.9 from baseline), compared with a mean functional assessment score of 84.1 (mean improvement 48.5) in the Arthrodesis patients. Cartiva subjects' FAAM Sports scores were substantially better at Week 2 and Week 6 but substantially worse at Month 6 and Month 12, which was the pre-specified primary success evaluation time point.

Table 33: FAAM Sports– Completed That Did Not Have Secondary Surgery [CARTIVA Table]

	Cartiva® Total Score						Fusion Total Score						t-test	Wilcoxon	Effect
	N	Mean	SD	Med	Min	Max	N	Mean	SD	Med	Min	Max	p-value[1]	p-value[2]	Size[3]
Baseline	127	36.9	20.9	34.4	0.0	100.0	50	35.6	20.5	31.3	0.0	87.5	0.694	0.505	0.07
Week 2	127	18.4	18.3	12.5	0.0	75.0	47	7.8	12.4	3.1	0.0	46.9	0.000	0.000	0.63
Week 6	126	39.5	26.3	37.5	0.0	100.0	49	22.4	22.5	18.8	0.0	81.3	<.0001	0.000	0.68
Month 3	123	55.1	26.5	59.4	0.0	100.0	46	53.9	29.5	56.3	0.0	100.0	0.804	0.853	0.04
Month 6	120	66.6	26.3	71.9	3.1	100.0	42	78.6	23.8	87.5	6.3	100.0	0.010	0.005	-0.47
Month 12	120	75.8	24.8	81.3	3.6	100.0	43	84.1	16.9	90.6	37.5	100.0	0.043	0.098	-0.37
Month 24	113	79.5	24.6	90.6	3.1	100.0	41	82.7	20.5	90.6	34.4	100.0	0.461	0.437	-0.14

Notes:
[1] Two sample pooled t-test p-value
[2] Two sample Wilcoxon rank sum test p-value
[3] Standardized effect size (group difference in means divided by pooled within group SD).

In Table 34 below, one can see similar results when examining the change from baseline. Both groups have declined function at Week 2, but the Cartiva group has returned to baseline by Week 6. By Month 3, the groups demonstrate similar improvements in function, and, by Month 6 and 12, the Arthrodesis group demonstrated substantially better function scores. The difference in mean change from baseline in FAAM Sports at 12 months (the pre-specified primary time point) between Cartiva and Arthrodesis was 11 points, where the sponsor considered a 9 point difference to be clinically meaningful. At 24 months, the difference in the average change from baseline was 7 points.

Table 34: FAAM Sports Change from Baseline – Completed That Did Not Have Secondary Surgery [CARTIVA Table]

	Cartiva® Total Score						Fusion Total Score						t-test	Wilcoxon	Effect
	N	Mean	SD	Med	Min	Max	N	Mean	SD	Med	Min	Max	p-value[1]	p-value[2]	Size[3]
Week 2	124	-19.0	22.0	-18.8	-75.0	53.6	47	-28.1	23.5	-25.0	-84.4	15.6	0.019	0.060	0.41
Week 6	124	1.7	28.3	0.0	-65.6	89.3	49	-13.3	19.4	-12.5	-75.0	25.0	0.001	0.002	0.58
Month 3	122	17.7	24.5	20.1	-43.8	100.0	46	19.1	24.8	15.0	-22.3	78.1	0.740	0.887	-0.06
Month 6	119	28.7	25.2	25.0	-37.5	100.0	42	43.0	23.7	46.9	-22.3	84.4	0.002	0.000	-0.58
Month 12	119	37.9	27.2	37.5	-25.0	100.0	43	49.0	21.7	53.1	3.1	100.0	0.018	0.017	-0.43
Month 24	112	41.2	28.3	40.8	-34.4	100.0	41	48.4	25.5	46.9	-12.9	100.0	0.152	0.159	-0.26

Notes:
[1] Two sample pooled t-test p-value
[2] Two sample Wilcoxon rank sum test p-value
[3] Standardized effect size (group difference in means divided by pooled within group SD).

The FAAM Sports analyzed as a responder analysis only shows a significant difference at Week 6, and that is in favor of the Cartiva group.

However, the Agency was concerned regarding the utility of using FAAM Sports outcomes measure as pre-defined by the sponsor to demonstrate device effectiveness. Three notable concerns can lead to bias in interpretation. The first is the applicability of using FAAM Sports to measure an individual's functional outcome as an *a priori* analysis. Second, content validity cannot be assumed without the use of the instrument, both *a priori* and post-hoc, as a whole. Third, because baseline scores may vary among individuals, it is difficult to understand true success, when only pre-operative to post-operative changes are considered.[18] In interactive discussions with the sponsor, and at the request of the Agency, the primary endpoint was revised to consider FAAM ADL rather than FAAM Sports.

This Sports measurement of function is consistent with the ADL measure of function discussed below. Both endpoints show superiority for Cartiva at 6 weeks and superiority for Arthrodesis at 6 months and 1 year, where the 1 year FAAM Sports was the pre-specified measure for function in the primary endpoint. As an 9-point change was pre-specified to be a clinically meaningful change, all three differences would be considered clinically significant[19].

[18] Guidance for Industry Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims
[19] Rathi, V.K. et.al; JAMA. 2015;314(6):604-612

Table 35: FAAM Sports Responder Analysis –Completed without secondary surgery [CARTIVA Table]

	Cartiva			Fusion			
	N	n	%	N	n	%	p-value[1]
Week 2	124	9	7.3%	47	1	2.1%	0.288
Week 6	124	48	38.7%	49	5	10.2%	0.000
Month 3	122	82	67.2%	46	29	63.0%	0.715
Month 6	119	94	79.0%	42	39	92.9%	0.056
Month 12	119	101	84.9%	43	42	97.7%	0.026
Month 24	112	97	86.6%	41	39	95.1%	0.243

Notes: [1] Fisher's Exact test

10.2.2.2 FAAM-ADL

FAAM ADL scores were used to evaluate each subject's improvement in functional activities of daily living, originally as a secondary endpoint. Questionnaires were completed prior to treatment, and at 2 and 6 weeks, and 3, 6, 12, and 24 months, post-operatively. Success in each category was defined as maintenance or improvement in status postoperatively as compared to the pre-operative condition.

For overall ADL function, at month 12, the Cartiva patients reported a mean overall functional assessment score of 88.6 (mean improvement of 29.1 from baseline), compared with a mean functional assessment score of 94.1 (mean improvement 37.4 in the Arthrodesis patients. Cartiva was substantially better than Arthrodesis at Week 2 and Week 6 ($p<0.05$), but Arthrodesis was substantially better at Month 6 and Month 12.

Table 36: FAAM ADL – Completers Without Secondary Surgery [CARTIVA Table]

	Cartiva® Total Score						Fusion Total Score						t-test	Wilcoxon	Effect
	N	Mean	SD	Med	Min	Max	N	Mean	SD	Med	Min	Max	p-value[1]	p-value[2]	Size[3]
Baseline	129	59.4	16.9	58.3	7.1	100.0	50	56.0	16.8	54.9	22.6	95.2	0.222	0.152	0.21
Week 2	126	48.8	21.6	47.6	2.4	100.0	47	40.3	20.7	39.3	7.5	84.2	0.021	0.023	0.40
Week 6	126	69.0	19.0	69.6	19.0	100.0	48	59.6	24.8	63.1	10.7	100.0	0.008	0.032	0.46
Month 3	125	77.3	17.7	80.0	36.9	100.0	46	82.5	14.9	86.9	41.7	100.0	0.079	0.110	-0.31
Month 6	123	82.7	17.5	88.1	22.6	100.0	43	89.9	12.4	95.2	50.0	100.0	0.014	0.010	-0.44
Month 12	123	88.6	14.4	95.0	27.4	100.0	43	94.1	6.8	95.2	71.4	100.0	0.017	0.066	-0.43
Month 24	116	90.4	15.0	96.4	29.8	100.0	41	94.6	7.1	96.4	69.0	100.0	0.082	0.524	-0.32

Notes:
[1] Two sample pooled t-test p-value
[2] Two sample Wilcoxon rank sum test p-value
[3] Standardized effect size (group difference in means divided by pooled within group SD).

Looking at the change from baseline results, one can see similar results. It is expected that the arthrodesis group would have lower function at Weeks 2 and 6, as these subjects may still be required to wear a boot. Arthrodesis subjects have greater function at every other time point from Month 3 to Month 24.

Table 37: FAAM ADL Change from Baseline Over Time [CARTIVA Table]

	Cartiva® Total Score						Fusion Total Score						t-test	Wilcoxon	Effect
	N	Mean	SD	Med	Min	Max	N	Mean	SD	Med	Min	Max	p-value[1]	p-value[2]	Size[3]
Week 2	125	-10.9	22.6	-10.0	-61.9	92.9	47	-16.1	20.7	-14.3	-73.8	22.0	0.167	0.235	0.24
Week 6	125	9.7	20.0	6.0	-33.3	92.9	48	3.3	22.0	3.9	-54.0	48.8	0.067	0.143	0.31
Month 3	125	17.6	17.6	16.3	-17.9	92.9	46	26.8	16.0	28.6	-9.5	53.6	0.002	0.001	-0.54
Month 6	122	23.1	18.9	22.7	-15.6	92.9	43	32.8	15.7	34.5	-1.2	63.1	0.003	0.001	-0.54
Month 12	122	29.1	18.4	28.6	-9.5	92.9	43	37.4	16.1	37.9	4.8	70.2	0.009	0.006	-0.47
Month 24	115	31.4	18.4	31.0	-16.7	92.9	41	38.1	19.0	41.4	-8.3	73.6	0.048	0.022	-0.36

Notes:
[1] Two sample pooled t-test p-value
[2] Two sample Wilcoxon rank sum test p-value
[3] Standardized effect size (group difference in means divided by pooled within group SD).

The responder analysis for FAAM ADL allows subjects to be a responder as long as their function did not decrease by more than 8 points. As this is a low bar for success, almost all subjects are responders by Month 3.

Table 38: FAAM ADL Responder Analysis for Function Over Time [CARTIVA Table]

	Cartiva			Fusion			
	N	n	%	N	n	%	p-value[1]
Week 2	125	56	44.8%	47	15	31.9%	0.164
Week 6	125	103	82.4%	48	36	75.0%	0.290
Month 3	125	118	94.4%	46	45	97.8%	0.684
Month 6	122	116	95.1%	43	43	100.0%	0.341
Month 12	122	121	99.2%	43	43	100.0%	1.000
Month 24	115	113	98.3%	41	40	97.6%	1.000

Notes: [1] Fisher's Exact test

The FDA considered other definitions of a responder, such as a 10 point improvement in FAAM scores. However, some subjects began the study with function scores of 90 or above. A subject whose function improves from a function of 95 to a function of 100 would be considered a failure under this approach.

Question for the Panel: In examining change from baseline FAAM ADL scores, Arthrodesis subjects performed better than Cartiva subjects at every time point from Month 3 to Month 24. Arthrodesis was also substantially better for the pre-specified primary functional assessment, FAAM Sports at Month 12. The responder analysis shows non-inferiority, but to be a responder the only requirement is to not worsen in terms of function. Does the Panel consider the definition of a responder to be appropriate,

and, based on the response, does the Panel consider the Cartiva group to be non-inferior to the Arthrodesis group in terms of function?

10.2.3 Freedom from SSSI

Freedom from subsequent secondary surgical interventions (SSSIs) was designated by the sponsor as part of a safety endpoint that also served as one component of the single composite primary endpoint for pain, function and safety (and denoted in the PMA as a "primary efficacy endpoint"). SSSIs were previously discussed in Section 9.4 in the context of the respective safety profiles for the Cartiva device and Arthrodesis control treatment groups. In this section, SSSIs are discussed in the context of assessments of the composite primary endpoint.

Secondary surgical procedures were documented to include revisions, removals, reoperation, and/or supplemental fixations over 24 months. The definitions for SSSIs were applied as outlined in the FDA's Guidance document, "Clinical Data Presentations for Orthopedic Device Applications".

SSSI were determined as to whether or not, for example, a secondary surgical procedure was required to treat non-unions and to remove broken hardware in fusion subjects and to address mechanical failure, device fracture, or device dislodgement in Cartiva subjects. The major complications associated with Cartiva and listed as part of their Risk Analysis included implant fracture or dislocation, any additional surgical interventions for the purpose of addressing development of osteonecrosis caused by the implant, and conversion to arthrodesis or any other implant revision surgical procedure.

From the sponsor's analysis, there were a total of 23 (23/202; 11%) of subjects who underwent a SSSI, with a similar incidence between groups (11% Cartiva and 12% Arthrodesis). This includes 4 roll-in subjects, but it does not include the 4 SSSI events among Cartiva subjects that occurred after 24 months. Thus, the estimate of the true rate of SSSI in the Cartiva group may be up to 14%. A total of 14 (9.2%) Cartiva subjects and 4 (8%) arthrodesis subjects had the implant and/or hardware removed during the course of the study. A total of 13 Cartiva patients and 6 Fusion patients had an SSSI defined by the sponsor and were considered failures for the primary endpoint.

Table 39: SSSI Events Until Month 24 [Cartiva Table]

SSSI	Cartiva® Roll-In (n=22)	Cartiva® Randomized (n=130)	Cartiva® Total (n=152)	Fusion (n=50)
Removal	4 (18.2%)	10 (7.7%)	14 (9.2%)	4 (8%)
Reoperation	0	1 (0.8%)	1 (0.7%)	0
Revision	0	1 (0.8%)	1 (0.7%)	3 (6%)
Supplemental Fixation	0	1 (0.8%)	1 (0.7%)	0
Overall	**4 (18.2%)**	**13 (10.0%)**	**17 (11.2%)**	**6[1] (12.0%)**

[1]One Fusion subject (02-031) experienced two events (one removal and one revision).

The sponsor does not consider in their SSSI events "other" secondary surgeries that occurred in parts of the body other than the foot that was initially treated with Cartiva or Arthrodesis. The FDA found 12 secondary surgical events that impacted the lower extremities, which could have impacted the

assessment of pain and function. For example, one Cartiva subject received the Cartiva device in their previously non-treated foot. Several others received treatment in the non-treated foot, another subject had knee surgery, etc. All except one occurred within the first 12 months after surgery.

These "other" secondary surgeries were performed on 7 Cartiva subjects (two of which were roll-in subjects) and 5 Arthrodesis subjects. Many of these subjects were already considered failures for other reasons, but if all of the "other" secondary surgeries were counted as failures, this would lead to 3 Cartiva and 2 Arthrodesis subjects that are considered successes in the primary endpoint as being failures. This would drop the lower bound of the non-inferiority confidence interval to 9%.

While the rates of SSSI appear similar, the reasons for SSSI and the types of incidents are not the same. Most of the Cartiva subjects were converted to arthrodesis while most of the arthrodesis subjects had their original hardware removed and no new hardware placed. The amount of pain and the level of function of these subjects were quite different, as seen in Table 40 below.

Table 40: Pain and Function Scores for Subjects That Had SSSI Events [FDA Table, Post-Hoc Analysis]

Time point	Cartiva (n=13)		Arthrodesis (n=6)	
	VAS	FAAM ADL	VAS	FAAM ADL
Baseline	71	59	72	56
3 months	39	65	9	84
6 months	50	70	4	85
1 year	40	70	7	94
2 years	12	87	4	96

The Arthrodesis subjects that had SSSI events experienced less pain and greater function than Cartiva subjects with SSSI events.

For three Arthrodesis subjects, all at site 2, the reason for the procedure was listed as "Hardware removed as an elective procedure, no failure or dislocation." These subjects represent half of the arthrodesis SSSI failures. If these elective procedures are not counted as failures, then the overall primary endpoint would not demonstrate non-inferiority at the 15% level.

Table 41: Sensitivity Analysis Where Elective Surgeries Are Removed From Primary Endpoint [FDA Table, Post-Hoc analysis]

Analysis Group	Cartiva	Arthrodesis	Lower Bound of one-sided 95% Confidence Interval
Primary – Completers	103/129 (79.8%)	40/47 (85.1%)	-15.6%

The median time to SSSI was 157days in the arthrodesis group and 364 days in the Cartiva group, or approximately 6 months and 1 year respectively. (This does not include the Cartiva SSSI events that occurred after the final follow-up at 24 months.)

Question for the Panel: The rate of SSSI events among randomized Cartiva subjects through 24 months was 10%. This does not include the 18% of roll-in subjects and does not include 4 SSSI events that occurred after 24 months. Meanwhile, half of the Arthrodesis SSSI procedures were elective, , all done at one site. If all Cartiva events are included and non-serious Arthrodesis events are excluded, this leads to estimated rates of SSSI of 14% for Cartiva and 6% for Arthrodesis. Does the Panel believe the risk of SSSI events in Cartiva is non-inferior to the risk of SSSI events in Arthrodesis?

10.2.4 Radiographic Endpoints

Freedom from radiographic findings of device displacement, device fragmentation and/or development of avascular necrosis for the Cartiva device and freedom from radiographic findings of mal-union, non-union and/or hardware failure was designated by the sponsor as part of a safety endpoint that also served as one component of the single composite primary endpoint for pain, function and safety (and denoted in the PMA as a "primary efficacy endpoint"). Radiographic findings were previously discussed in Section 9.5 in the context of the respective safety profiles for the Cartiva device and Arthrodesis control treatment groups. In this section, radiographic findings are discussed in the context of assessments of the composite primary endpoint.

Radiographic assessments, as utilized in the safety component of the composite primary endpoint, were performed at 24 months by an independent review of plain radiographs. Plain radiographs allowed for the assessment of abnormal bone formation at the fusion site in Arthrodesis subjects and loss of implant integrity with the Cartiva device.

Qualitative evaluations included heterotopic ossification (HO), radiolucency, bony fractures, avascular necrosis (AVN), adverse bony reactions, device displacement, fusion status, device integrity, and additional observations.

Due to the differences in the intended mechanism of action of Cartiva and arthrodesis, the two groups were examined for different radiographic outcomes. The Cartiva subjects were deemed as failures if there was device displacement, device fragmentation and/or development of avascular necrosis, whereas the Arthrodesis subjects were deemed as failures if there was mal-union, non-union and/or hardware failure.

The examination of the radiographs did not determine any Cartiva subjects to be radiographic failures, and the sponsor determined that 5 (10%) of the Arthrodesis subjects were radiographic failures. Table 42 below summarizes the radiographic findings.

Table 42: All Radiographic Findings [CARTIVA Table]

Radiographic Finding	Cartiva® SCI Randomized (n=130)		Cartiva® SCI Safety (n=152)		Arthrodesis (n=50)	
	n	%	n	%	n	%
Radiographic Failure Modalities in Primary Endpoint						
Avascular Necrosis	0	0.0%	0	0.0%	0	0.0%
Device Displacement	0	0.0%	0	0.0%	--	--
Device Fragmentation	0	0.0%	0	0.0%	--	--

Non Union	--	--	--	--	4	8.0%
Mal Union	--	--	--	--	0	0.0%
Fractured Hardware	--	--	--	--	1	2.0%
Other Radiographic Findings						
Fusion (Cartiva® cohort)	0	0.0%	0	0.0%	--	--
Radiolucency (any)	5	3.8%	6	3.9%	5	10.0%
Bony Fracture	1	0.8%	1	0.7%	1	2.0%
Bony Reaction	64	49.2%	75	49.3%	3	6.0%
Heterotopic Ossification	75	57.7%	89	58.6%	24	48.0%

The Cartiva group has much higher rates of Bony Reactions, 49% Cartiva and 6% Arthrodesis, and Class 1-3 Heterotopic Ossification, 53% Cartiva and 4% Arthrodesis (Class 4 is expected in Arthrodesis subjects). As with the three Arthrodesis subjects that were only radiographic failures that are discussed below in conjunction with Table 50, there is no evidence within the study that the radiographic findings cited above led to poor outcomes. Nonetheless, this serves as an example of differences in the radiographic standard for the investigative and control groups introducing challenges to the interpretation of this analysis.

In Table 42 above, all types or severities of Bony Reactions are grouped together. However, only the most extreme Bony Reactions represent a concern. The Agency is specifically concerned with osteolysis.

Table 43: Incidence of Bony Reactions [Cartiva]

Bony Reaction	Cartiva® SCI Randomized (n=130)		Cartiva® SCI Safety (n=152)		Fusion (n=50)	
	n	%	n	%	n	%
Erosion	2	1.5%	3	2.0%	0	0.0%
Cystic Changes	26	20.0%	30	19.7%	0	0.0%
Loss of Cortical White	35	26.9%	40	26.3%	0	0.0%
Osteolysis	2	1.5%	3	2.0%	3	6.0%
Any Bony Reaction[1]	**64**	**49.2%**	**75**	**49.3%**	**3**	**6.0%**
No Bony Reaction	**66**	**50.8%**	**77**	**50.7%**	**47**	**94.0%**

[1]Subject 06-005 had both loss of cortical white and osteolysis at different time points.

If all osteolysis subjects are considered failures, then 2 Cartiva successes would be considered failures. As two of the Arthrodesis subjects were already failures, then only 1 additional Arthrodesis subject would be considered a failure. This would lead to a lower bound of the non-inferiority confidence interval of -10.1%.

The independent core lab, Medical Metrics, Inc., provided qualitative measurements of heterotopic ossification via independent radiographic review using the following categories:

- **None**: No evidence heterotopic bone formation
- **Class 1**: Islands of bone within the soft tissue about the MTP joint

- **Class 2**: Bone spurs contiguous with the distal first metatarsal, proximal phalanx of the great toe or sesamoid bones which do not contact or nearly contact adjacent bones or bone spurs.
- **Class 3**: Bone spurs from the distal first metatarsal, proximal phalanx of the great toe or sesamoid bones which contact or nearly contact each other but do not appear fused
- **Class 4**: Apparent bone ankylosis of the MTP joint

Not all classes of Heterotopic Ossification are equally concerning. The Agency is particularly concerned with Class 3 Heterotopic Ossification in the Cartiva group. (If Cartiva subjects had experienced Class 4 Heterotopic Ossification, this would have also been concerning.)

Table 44: Incidence of Heterotopic Ossification [Cartiva]

Heterotopic Ossification	Cartiva® SCI Randomized (n=130)		Cartiva® SCI Safety (n=152)		Fusion (n=50)	
	n	%	n	%	n	%
Class 1	21	16.2%	29	19.1%	1	2.0%
Class 2	63	48.5%	70	46.1%	1	2.0%
Class 3	11	8.5%	13	8.6%	0	0.0%
Class 4	0	0.0%	0	0.0%	22	44.0%
Any Heterotopic Ossification	**75***	**57.7%**	**89***	**58.6%**	**23**	**46.0%**
No Heterotopic Ossification	**55**	**42.3%**	**63**	**41.4%**	**27**	**54.0%**

*19 Cartiva® subjects had different grades of heterotopic ossification at different time points.

All 11 randomized Cartiva subjects with Class 3 Heterotopic Ossification were considered successes. If they were switched to failures, the lower bound of the non-inferiority confidence interval would have been -19.2%. This raises the question as to whether the sponsor has utilized consistent assessment criteria for radiographic failures for the Cartiva treatment and Arthrodesis control groups, particularly when compared to the criteria applied by the sponsor in determining three Arthrodesis subjects with excellent pain and function scores at one and two years to be failures solely based on a poor radiographic outcome.

The three Arthrodesis subjects that were deemed failures due only to radiographic findings are listed in Table 45 below. Two of the five Arthrodesis subjects that were radiographic failures were also deemed surgical failures, as they had their device removed or replaced.

Table 45: Pain and Function scores for subjects that were radiographic failures only [FDA Table]

Subject*	Reason for Failure	VAS			FAAM ADL		
		6 months	1 year	2 year	6 months	1 year	2 years
1	Non-union	75	2	0	56	81	95
2	Device fracture	0	0	0	100	100	100
3	Non-union	17	31	9	90	90	96

* Subject IDs were redacted throughout in order to protect patient privacy

These three Arthrodesis subjects all had excellent pain and function scores at one and two years without having any intervention. It is not clear, for example, why Subject 2, who had excellent pain and function scores, should nonetheless be considered a failure as opposed to a Cartiva subject with bony reactions and heterotopic ossification, but was considered a success. Furthermore, there is no evidence within the 24 month study that these radiographic findings would necessarily lead to poor overall outcomes, as they were not correlated with increases in pain or loss of function. This raises a question regarding how appropriate are the radiographic assessment criteria for both groups.

This part of the primary endpoint for radiographic findings was pre-specified, and it is typical in orthopedic studies to include this type of endpoint. Still, because of the difference in the application of this part of the composite endpoint, it is reasonable to look at a sensitivity analysis where this is not part of the primary endpoint. As can be seen in the table below, if radiographic success/failure is not included, then Cartiva would not be able to demonstrate non-inferiority at the 15% level.

Table 46: Sensitivity Analysis Where Radiographs Are Removed From Primary Endpoint [FDA Table, Post-Hoc analysis]

Analysis Group	Cartiva	Arthrodesis	Lower Bound of one-sided 95% Confidence Interval
Primary - Completers	103/129 (79.8%)	40/47 (85.1%)	-15.6%

Question for the Panel: The two devices have different standards for determining radiographic success or failure. Are the radiographic standards appropriate for each device? If not, what radiographic standards are recommended?

10.3 Secondary Endpoints

As mentioned previously, the secondary endpoints were pre-specified to be tested in a specific order, and VAS was to be tested first. As VAS was not significant in favor of Cartiva (instead it was significant in favor of Arthrodesis), the other secondary endpoints cannot be formally tested, but it is still useful to discuss these endpoints.

10.3.1 Active Peak Dorsiflexion Angles

From the evaluation of active peak dorsiflexion, the sponsor concludes that Arthrodesis subjects lost about 8 degrees (36%) of this motion compared to Cartiva subjects who gained a mean of 5 degrees (21%) from baseline. The sponsor claims that retention of this motion by the device is an important benefit that the patient would consider in order to maintain toe push-off or flexion required for certain 'demands activities" or selection of shoe wear. In addition, the sponsor claims that the device provides an alternative treatment to the Arthrodesis procedure, which permanently restricts motion.

Table 47 below demonstrates a descriptive analysis of active peak dorsiflexion angles by treatment group over time in the pre-specified mITT LOCF population.

Table 47: Active Peak Dorsiflexion Angles **[CARTIVA Table]**

Visit	Cartiva Mean (SD) N Med (Min, Max)	Arthrodesis Mean (SD) N Med (Min, Max)	P-value
Baseline	22.67 (11.193) 130 20 (0, 58)	22.88 (11.162) 50 20 (5, 50)	0.9100[1]
2 Weeks	20.75 (10.166) 130 20 (0, 40)	13.02 (8.436) 50 10 (0, 32)	<0.0001[1]
6 Weeks	25.15 (10.801) 130 25 (5, 55)	12.64 (9.053) 50 12 (0, 26)	<0.0001[1]
3 Months	26.62 (11.599) 130 26 (0, 60)	13.24 (9.720) 50 13 (0, 30)	<0.0001[1]
6 Months	27.61 (10.044) 130 30 (5, 60)	14.48 (8.517) 50 15 (0, 30)	<0.0001[1]
1 Year	28.24 (11.331) 130 30 (5, 60)	15.30 (7.451) 50 15 (0, 35)	<0.0001[2]
2 Year	27.43 (12.346) 130 30 (5, 60)	14.74 (8.256) 50 15 (0, 35)	<0.0001[2]

[1]Two-sided equal variance t-test
[2]Two-sided unequal variance t-test

The implied benefit is that a subject will have increased function by using the Cartiva device. However, based on the study results, it is not clear that this premise is supported by the data; the Cartiva subjects may actually have less function in the long run when compared to Arthrodesis subjects.

Question for Panel: Prospective subjects will likely have the impression that increased mobility will allow for greater function in Cartiva as compared to arthrodesis. However, the level of function for Cartiva appears to be the same or worse than arthrodesis from 3 months to 2 years. Does the Panel have any suggestions to ensure that prospective subjects are properly educated and able to make informed decisions with regards to the functionality of the devices? Can the Panel provide a discussion on how best to objectively capture patient preferences with regards to the retention of first MTPJ motion?

10.3.2 Quality-of-Life Assessments

SF-36 - Quality-of-life was assessed using the SF-36 Physical Functioning Scale and the Foot Function Index Revised (FFI-R) questionnaires. Questionnaires were completed prior to treatment, and at 2 and 6 weeks, and 3, 6, 12, and 24 months, post-operatively. Success in each category was defined as maintenance or improvement in status postoperatively as compared to the pre-operative baseline condition.

The mean improvement in SF-36 from pre-op to 12 months after surgery for the investigational group was 26.5, compared to 32.6 for the control group. The mean SF-36 scores at each time point can be seen in Table 52 below. As was seen with the FAAM endpoints, the Cartiva group was significantly

better at Week 6 and the Arthrodesis group was significantly better at Month 6. The Arthrodesis group did better, but not significantly better, at 1 and 2 years.

Table 48: SF-36 – Completers without secondary surgery [CARTIVA Table]

	Cartiva Total Score						Fusion Total Score						t-test	Wilcoxon	Effect
	N	Mean	SD	Med	Min	Max	N	Mean	SD	Med	Min	Max	p-value[1]	p-value[2]	Size[3]
Baseline	130	52.4	22.8	50.0	0.0	100.0	50	49.8	23.6	40.0	15.0	100.0	0.499	0.352	0.11
Week 6	128	60.7	23.7	60.0	10.0	100.0	49	44.7	26.8	40.0	0.0	100.0	0.000	0.000	0.66
Month 3	128	68.1	25.2	75.0	5.0	100.0	46	71.7	25.5	80.0	0.0	100.0	0.405	0.353	-0.14
Month 6	124	72.3	26.3	80.0	0.0	100.0	43	82.8	22.4	90.0	5.0	100.0	0.021	0.014	-0.41
Month 12	123	78.9	22.7	90.0	5.0	100.0	43	83.7	24.9	95.0	0.0	100.0	0.247	0.064	-0.21
Month 24	116	83.2	20.9	95.0	25.0	100.0	41	85.1	19.5	95.0	5.0	100.0	0.613	0.597	-0.09

Notes:
[1] Two sample pooled t-test p-value
[2] Two sample Wilcoxon rank sum test p-value
[3] Standardized effect size (group difference in means divided by pooled within group SD).

FFI-R - The Revised Foot Function Index is a subject reported questionnaire comprised of 5 subscales, which evaluate pain, stiffness, difficulty, activity limitation, and social issues. This scale is valid and a highly reliable assessment for subjects with foot problems.

Cartiva patients showed a mean total score of 11.3 (improvement from 42.5 at baseline), compared with 4.2 in the Control group (improvement from 45.4 at baseline). The difference in means FFI-R score was substantially better for Arthrodesis at every time point from Week 6 to Month 24.

Table 49: FFI-R – Completed Subjects Without Secondary Surgery [CARTIVA Table]

	Cartiva® Total Score						Fusion Total Score						t-test	Wilcoxon	Effect
	N	Mean	SD	Med	Min	Max	N	Mean	SD	Med	Min	Max	p-value[1]	p-value[2]	Size[3]
Baseline	130	42.5	15.3	40.0	8.0	80.0	50	45.4	16.8	43.4	11.4	94.3	0.279	0.374	-0.18
Week 2	129	33.2	20.3	32.0	0.0	95.0	49	30.5	19.0	30.0	0.0	74.3	0.429	0.571	0.13
Week 6	128	24.2	15.8	22.9	0.0	80.0	48	17.1	15.6	14.7	0.0	72.0	0.009	0.007	0.45
Month 3	128	20.5	13.2	20.0	0.0	56.0	46	14.3	11.5	11.7	0.0	36.0	0.006	0.009	0.48
Month 6	124	18.5	15.6	16.0	0.0	72.0	43	7.6	9.6	4.0	0.0	40.0	<.0001	0.000	0.76
Month 12	123	11.3	14.4	8.0	0.0	80.0	43	4.2	6.2	2.9	0.0	20.0	0.002	0.002	0.56
Month 24	116	8.7	13.5	2.9	0.0	68.0	41	3.9	7.8	0.0	0.0	34.3	0.032	0.015	0.40

Notes:
[1] Two sample pooled t-test p-value
[2] Two sample Wilcoxon rank sum test p-value
[3] Standardized effect size (group difference in means divided by pooled within group SD).

10.3.3 Patient and Investigator Global Assessments

Subjects' response to the question "My overall well-being has improved since the beginning of the study?" with five possible answers (Strongly agree, Agree, Neither agree nor disagree, Disagree, and Strongly disagree) are analyzed. The sponsor combines the Strongly Agree and Agree answers together to conclude that the results are similar between groups at 12 months, with 75% of Cartiva improved compared to 79% of Arthrodesis subjects.

Although a substantially greater percentage of Arthrodesis subjects (85%) are improved at 24 months compared to the Cartiva group (74%), the sponsor concludes that both groups demonstrate durability of improvement. However, it is concerning that, at 6, 12, and 24 months, there are substantially greater percentages (15 to 20%) of Arthrodesis subjects with the "Strongly Agree" response to improvement when compared with Cartiva. There are similar trends seen with the Investigator Global Assessment, except at 24 months, where 5% more investigators strongly agreed that the Cartiva group had improved the overall well-being of the subjects.

A summation table for the Patient Global Assessment as originally assessed by study visit and treatment group is provided below.

Table 50: Patient Global Assessment by Visit [CARTIVA Table]

Visit	Score	Cartiva x/n (%)	Arthrodesis x/n (%)	P-value[1]
Week 2	1 Strongly Agree	13/130 (10.00)	1/47 (2.13)	0.1033
	2 Agree	41/130 (31.54)	13/47 (27.66)	
	3 Neither Agree nor Disagree	67/130 (51.54)	29/47 (61.70)	
	4 Disagree	4/130 (3.08)	4/47 (8.51)	
	5 Strongly disagree	5/130 (3.85)	0/47 (0.00)	
Week 6	1 Strongly Agree	23/128 (17.97)	6/50 (12.00)	0.4834
	2 Agree	45/128 (35.16)	25/50 (50.00)	
	3 Neither Agree nor Disagree	43/128 (33.59)	13/50 (26.00)	
	4 Disagree	14/128 (10.94)	5/50 (10.00)	
	5 Strongly disagree	3/128 (2.34)	1/50 (2.00)	
Month 3	1 Strongly Agree	24/130 (18.46)	12/48 (25.00)	0.5996
	2 Agree	62/130 (47.69)	25/48 (52.08)	
	3 Neither Agree nor Disagree	32/130 (24.62)	8/48 (16.67)	
	4 Disagree	10/130 (7.69)	3/48 (6.25)	
	5 Strongly disagree	2/130 (1.54)	0/48 (0.00)	
Month 6	1 Strongly Agree	36/125 (28.80)	22/47 (46.81)	0.1307
	2 Agree	48/125 (38.40)	17/47 (36.17)	
	3 Neither Agree nor Disagree	30/125 (24.00)	6/47 (12.77)	
	4 Disagree	11/125 (8.80)	2/47 (4.26)	
	5 Strongly disagree	0/125 (0.00)	0/47 (0.00)	
Month 12	1 Strongly Agree	43/130 (33.08)	25/47 (53.19)	0.1074
	2 Agree	54/130 (41.54)	12/47 (25.53)	
	3 Neither Agree nor Disagree	24/130 (18.46)	9/47 (19.15)	
	4 Disagree	7/130 (5.38)	1/47 (2.13)	

	5 Strongly disagree	2/130 (1.54)	0/47 (0.00)	
Month 24	1 Strongly Agree	49/126 (38.89)	26/47 (55.32)	0.2821
	2 Agree	44/126 (34.92)	14/47 (29.79)	
	3 Neither Agree nor Disagree	24/126 (19.05)	5/47 (10.64)	
	4 Disagree	6/126 (4.76)	2/47 (4.26)	
	5 Strongly disagree	3/126 (2.38)	0/47 (0.00)	

[1]Two-sided Kruskal-Wallis test

The Patient Global Assessment supports that up to 20% more patients in the Arthrodesis group at 12 and 24 months "Strongly Agree" that their overall well-being has improved compared with those who received the Cartiva device. Table 51 below combines the "Strongly Agree" and "Agree" responses and demonstrates that even looking at the two combined, the sponsor cannot claim non-inferiority between Cartiva and Arthrodesis for this endpoint.

Table 51: Patients' assessments of if their overall well-being has improved at each time point– Percent Agreed or Strongly Agreed [FDA TABLE]

Time point	Cartiva	Arthrodesis	Difference (C-A)	Lower Bound of C.I.
2 weeks	53/130 (41%)	15/48 (31%)	10%	-3.5%
6 weeks	68/129 (53%)	31/49 (63%)	-10%	-24.0%
3 months	86/130 (66%)	37/48 (77%)	-11%	-23.0%
6 months	85/126 (67%)	38/46 (83%)	-16%	-26.6%
1 year	97/130 (75%)	37/47 (79%)	-4%	-15.8%
2 years	94/128 (73%)	40/47 (85%)	-12%	-22.4%

The investigators were asked the same question as the subjects, and the Arthrodesis group had substantially more ratings of "Strongly Agree" and "Agree" at both 3 and 6 months. There were no substantial differences at 1 year or 12 months.

Table 52: Investigators' Global Assessment [CARTIVA Table]

Visit	Score	Cartiva x/n (%)	Arthrodesis x/n (%)	P-value[1]
Week 2	1 Strongly Agree	5/129 (3.88)	1/50 (2.00)	0.8250
	2 Agree	26/129 (20.16)	10/50 (20.00)	
	3 Neither Agree nor Disagree	88/129 (68.22)	37/50 (74.00)	
	4 Disagree	8/129 (6.20)	2/50 (4.00)	
	5 Strongly disagree	2/129 (1.55)	0/50 (0.00)	
Week 6	1 Strongly Agree	13/129 (10.08)	3/50 (6.00)	0.6647
	2 Agree	44/129 (34.11)	20/50 (40.00)	
	3 Neither Agree nor Disagree	56/129 (43.41)	24/50 (48.00)	
	4 Disagree	15/129 (11.63)	3/50 (6.00)	
	5 Strongly disagree	1/129 (0.78)	0/50 (0.00)	
Month 3	1 Strongly Agree	26/130 (20.00)	9/49 (18.37)	0.0095
	2 Agree	44/130 (33.85)	30/49 (61.22)	
	3 Neither Agree nor Disagree	51/130 (39.23)	8/49 (16.33)	
	4 Disagree	7/130 (5.38)	2/49 (4.08)	
	5 Strongly disagree	2/130 (1.54)	0/49 (0.00)	
Month 6	1 Strongly Agree	30/127 (23.62)	20/47 (42.55)	0.0257
	2 Agree	49/127 (38.58)	18/47 (38.30)	
	3 Neither Agree nor Disagree	33/127 (25.98)	9/47 (19.15)	
	4 Disagree	14/127 (11.02)	0/47 (0.00)	
	5 Strongly disagree	1/127 (0.79)	0/47 (0.00)	
Month 12	1 Strongly Agree	53/130 (40.77)	22/47 (46.81)	0.8207
	2 Agree	45/130 (34.62)	17/47 (36.17)	
	3 Neither Agree nor Disagree	25/130 (19.23)	7/47 (14.89)	
	4 Disagree	6/130 (4.62)	1/47 (2.13)	
	5 Strongly disagree	1/130 (0.77)	0/47 (0.00)	
Month 24	1 Strongly Agree	66/127 (51.97)	22/47 (46.81)	0.8330
	2 Agree	41/127 (32.28)	17/47 (36.17)	
	3 Neither Agree nor Disagree	14/127 (11.02)	7/47 (14.89)	
	4 Disagree	5/127 (3.94)	1/47 (2.13)	
	5 Strongly disagree	1/127 (0.79)	0/47 (0.00)	

[1]Two-sided Kruskal-Wallis test

10.3.3.1 Willingness to Have the Procedure Again

The subjects were asked at each time point if they would be willing to have the procedure again. The results are provided below in Table 53.

Table 53: Patients' willingness to have the procedure again [FDA TABLE]

Time point	Cartiva	Arthrodesis	Difference (C-A)	Lower Bound of C.I.
2 weeks	119/124 (96%)	43/47 (91%)	5%	-2.8%
6 weeks	115/126 (91%)	40/48 (83%)	8%	-1.8%
3 months	110/127 (87%)	42/48 (88%)	-1%	-10.2%
6 months	100/125 (80%)	40/46 (87%)	-7%	-17.0%
1 year	101/128 (79%)	39/47 (83%)	-4%	-14.9%
2 years	102/128 (80%)	36/47 (77%)	3%	-8.6%

Interestingly, both groups' willingness to have the procedure again peeked at the Week 2 visit when they were experiencing more pain and had less function than at baseline. This assessment reveals that both groups generally improved. It does not allow one to assess the magnitude of improvement. Subjects were not blinded and volunteered for a study where they were more likely to receive the Cartiva device, so interpretation of these types of endpoints is difficult.

10.3.3.2 Alternate Definition of Pain and Function Success

The following analysis of VAS and FAAM ADL was not specified in the protocol. It is a post-hoc assessment conducted by the FDA, acknowledging the potential limitations of such an assessment.

The maintenance of function pre-specified for FAAM success allows a subject to get slightly worse over time and still be a functional success. Yet specifying a certain number of points improvement in function is difficult because some subjects began the study with a high level of function. Similarly, under the pre-specified definitions of success for pain, a subject could have a VAS score over 60 and still be considered a success, as long as he/she had improved by 30% from baseline.

An alternative definition of success might be a minimal amount of pain and a high level of functioning. One possible definition of minimal pain is <20 on the VAS. One possible definition of a high level of functioning is a FAAM ADL score of 75 or greater. (If a subject marks "Slight Difficulty" on every item on the FAAM ADL questionnaire, then the subject will score a 75.) These definitions are post-hoc and the results below are robust to minor changes in the cutoffs.

Table 54: Alternative Definitions of Pain and Function Success [FDA TABLE, Post-Hoc Analysis]

Time Point	Cartiva			Arthrodesis		
	VAS <20	FAAM ADL >=75	Both	VAS <20	FAAM ADL >=75	Both
6 months	49%	78%	48%	85%	85%	76%
1 year	72%	81%	69%	87%	96%	83%
2 year	83%	90%	80%	94%	96%	91%

In creating these alternative definitions of a successful subject, it can be seen that the difference between the Arthrodesis group and Cartiva group is 11% at 24 months and 28% at 6 months.

11. CLINICAL STUDY DISCUSSION

The Cartiva device is intended for patients over the age of 18 years of age requiring surgical treatment for osteoarthritis of the first metatarsal. It is to be considered as an alternative to arthrodesis that results in loss of motion between the joint. The PMA includes data for 202 patients (152 Cartiva and 50 Arthrodesis) who completed the surgical procedure and were treated in the multicenter (12 sites), prospective, controlled clinical investigation of the Cartiva device as compared to arthrodesis. The clinical data provided in this application relates to short and mid-term safety and effectiveness data for the subject device.

Overall, there are questions regarding the PMA study primary endpoint, definition of success for each group, and methods of analysis of the primary endpoint for effectiveness.

To summarize, FDA has the following concerns that relate to interpreting safety and effectiveness of the Cartiva device and assessing its benefit/risk profile based on the clinical data set.

1. Evaluation of the composite primary endpoint is challenging because the assessment of success and failure as it relates to adverse events, secondary surgeries, and radiographic findings was not necessarily appropriately defined. The primary success analysis takes into account only certain pre-specified adverse events and radiographic findings that led to secondary surgeries and does not include all applicable device-related adverse events, secondary surgeries, or radiographic findings. See Sections 9.7, 10.2.3, and 10.2.4 for further discussion.

2. The clinical benefit observed in the investigational group is unclear based on the pre-specified primary composite endpoint at 12 months and based on the FDA-requested post-hoc primary composite endpoint analysis at 24 months when pain and functional outcomes are considered individually. These observations for the individual pain and function measures have potential ramifications on the overall clinical interpretation of results for the primary composite endpoint, particularly when examined in the context of questions regarding other components of the composite endpoint as discussed above. See Section 10.2 for further discussion.

3. The sponsor reports success of the Cartiva device in meeting the primary composite endpoint; that success was contingent upon the use of a 15% non-inferiority margin chosen by the sponsor for the study. In feedback provided to the sponsor prior to the oUS study, the Agency recommended the use of a non-inferiority margin corresponding to a maximum clinically insignificant difference in lieu of the 15% non-inferiority margin. A non-inferiority margin of 10% has typically been utilized in non-inferiority studies for other orthopedic implants. Whatever non-inferiority margin is utilized, FDA believes this margin should correspond to a maximum clinically insignificant difference for the investigative and control treatments. See Sections 7.1.7 and 10.1 for further discussion.

4. The ability to determine clinical success is made challenging by the use of some clinical outcome instruments, which are not based on categories widely accepted in the literature as clinically meaningful differences for the condition being treated. See Section 10.1 for further discussion.

5. The proposed target population for the Cartiva was identified as subjects with osteoarthritis Grades 2 to 4 of the first MTPJ. FAAM Sports is the pre-defined outcome instrument used to measure functional success. Because there were no objective measures of patient preference, the population for whom the device is intended is unclear. A quantitative approach to eliciting patient preferences should be considered.[20] See Section 10.3.1 for further discussion.

[20] Patient Preference Information – Submission, Review in PMAs, HDE Applications, and De Novo Requests, and Inclusion in Device Labeling Draft Guidance for Industry, Food and Drug Administration Staff, and Other Stakeholders

6. The sponsor is claiming a benefit of shorter rehabilitation and surgical procedure times. However, rehabilitation time and time to successful rehabilitation outcomes were not objectively measured or collected. Surgical procedure time was not available for 26 and 22 percent of Cartiva and Arthrodesis patients, respectively. Therefore, the current data have limitations regarding such questions of benefit. See Section 8.5 for further discussion.

7. The "all evaluated" accounting is not clear, and as such, the result may reflect a total study population that includes subjects either not eligible for the device or not treated as randomized. Additional protocol deviations should be considered in the PP analysis that has direct impact on determining safety and effectiveness outcomes. See Section 8.3 for further discussion.

8. Radiographic Outcome Considerations: The Agency understands that the Cartiva device, according to its risk analysis profile, is associated with certain radiographic outcomes that can impact its treatment effect. Accordingly, it is reasonable to consider that a radiolucency or heterotopic ossification at the operative level would impact the safety and effectiveness of the device. The sponsor conducted an analysis of radiographic findings. The Agency has the following concerns with the radiographic findings presented in the PMA application:

    a. *Bony Reactions:* There were bony cystic lesions noted upon radiographic review. Analyses comparing outcomes in subjects with and without these lesions were conducted by the sponsor, and the sponsor concluded that these radiographic findings had no clinical impact. The clinical significance of the observed cystic lesions remains unclear. See Section 9.6 for further discussion.

    b. *Heterotopic Ossifications:* The incidence of HO was reported by independent radiologists and was noted frequently in the Cartiva population. Furthermore, the location and impact on the surrounding anatomy were not included in the study protocol. While pain and function assessments for Cartiva subjects with Class 3 Heterotopic Ossification were not reported (and thus it is currently unknown whether Class 3 Heterotopic Ossification correlates with poorer outcomes with respect to pain and function), there are concerns that the frequency of these events noted in the midterm potentially could have longer-term clinical effects. See Sections 9.6 and 10.2.4 for further discussion.

12. BENEFIT/RISK ASSESSMENT

The Agency in stating the above concerns recognizes that the sponsor has conducted a non-inferior study with pre-defined measures for failure at the pre-specified 12 month and the requested post-hoc 24 month endpoints. However, there are challenges interpreting the individual clinical success rate, based on concerns regarding several components of the composite endpoint. The Agency has clinical concerns, as noted above, with the safety and overall benefit/risk profile of the device at this time and is concerned that additional information may be needed.

When making a determination of the benefit-risk profile of a device, the Agency considers the following:

- Benefits: type of benefits, magnitude of benefits, probability of the patient experiencing one or more benefits, and duration of effect

- Risks: types, number, and rates of harmful events associated with the use of the device (device-related serious, device-related non-serious, and procedure-related adverse events), probability of a harmful event, and duration of harmful events.

- Additional factors (if applicable): uncertainty, characterization of the disease, patient tolerance for risk and perspective on benefit, availability of alternate treatments, risk mitigation, post-market data, and novel technology addressing unmet needs.

12.1 Summary of Benefits

Over the course of the study, the following benefits were considered with use of the Cartiva device when compared to the Arthrodesis control group. These benefits should be interpreted in the context of the additional benefit-risk considerations, especially those of data uncertainty, presented in the Additional Considerations section below:

1. Improvement in VAS pain scores, with 88% and 89% responders in the Cartiva group at 12 and 24 months respectively, where a responder is defined as having a 30% decrease in VAS. The responder rate in the Arthrodesis control group was 100% and 98% at 12 and 24 months.

2. Maintenance of function as measured by FAAM Sports, with 98% and 96% responders at 12 and 24 months, where a responder is defined as not having worsened by more than 9 points from baseline. The responder rate in the Arthrodesis control group was 100% and 98% at 12 and 24 months. The Cartiva group was substantially better than the Arthrodesis group at Week 6 for this assessment.

3. Maintenance of function as requested and measured by FAAM ADL, with 99% and 98% responders at 12 and 24 months, where a responder is defined as not having worsened by more than 8 points from baseline. The responder rate in the Arthrodesis control group was 100% and 98% at 12 and 24 months. The Cartiva group was substantially better than the Arthrodesis group at Week 6 for this assessment.

4. Improvement in quality of life as measured by SF-36, with 89% and 94% responders at 12 and 24 months, where a responder is defined as having improved by 10 points from baseline. The responder rate in the Arthrodesis control group was 93% and 93% at 12 and 24 months. The Cartiva group was substantially better than the Arthrodesis group at Week 6 for this assessment.

5. Improvement in function as measured by FFI-R, with 94% and 95% responders in the Cartiva group at 12 and 24 months, where a responder is defined as having improved by 5 points from baseline. The responder rate in the Arthrodesis control group was 100% and 95% at 12 and 24 months.

6. General agreement at 12 and 24 months post-treatment with the patient satisfaction question, "My overall well-being has improved since the beginning of the study?" The proportion of subjects in the primary analysis dataset responding with answers of "strongly agree" or "agree" at 12 months was 75% for the Cartiva treatment group and 79% for the Arthrodesis group. At

24 months 74% of Cartiva subjects and 85% of Arthrodesis subjects responded with answers of "strongly agree" or "agree".

7. General agreement at 12 and 24 months post-treatment with the investigator's assessment of the satisfaction question, "My overall well-being has improved since the beginning of the study?" The proportion of subjects in the primary analysis dataset responding with answers of "strongly agree", or "agree" at 12 months was 75% for the Cartiva treatment group and 83% for the Arthrodesis group. At 24 months 84% of Cartiva subjects and 83% of Arthrodesis subjects responded with answers of "strongly agree" or "agree".

8. Maintenance of range of motion as measured by Active MTP Dorsiflexion. The Cartiva group showed substantially greater range of motion than the Arthrodesis group at all time points. However, as discussed in Section 10.3.1, this greater range of motion for Cartiva subjects did not appear to ultimately correlate with function assessments, which were substantially better for Arthrodesis subjects at longer time points.

9. Shorter surgery times, as the average procedure time was 23 minutes less in the Cartiva group. Data were not available for all subjects.

10. Lower rates of certain radiographic endpoints, such as non-union. However, such radiographic endpoints are not the goal of the Cartiva procedure.

12.2 Summary of Risks

Over the course of the study, the following risks were identified. These risks should be interpreted in the context of the additional benefit-risk considerations presented in the section below, especially those of data uncertainty, presented in the Additional Considerations section below:

1. The overall rate of any device related adverse event at 24 months was numerically higher in Cartiva as compared to the Arthrodesis control (Cartiva, 15.1%; Arthrodesis, 8.0%). The overall rate of any serious device related adverse event at 24 months was numerically higher in Cartiva as compared to the Arthrodesis control (Cartiva, 7.2%; Arthrodesis, 4.0%).

2. The rates of Bony Reactions, 49% Cartiva and 6% Arthrodesis, and Class 1-3 Heterotopic Ossification, 53% Cartiva and 4% Arthrodesis (Class 4 is expected in Fusion subjects) are higher in the Cartiva group as compared to the Arthrodesis control.

3. Subjects may require a secondary surgery if the Cartiva procedure is unsuccessful. The estimated rate of secondary surgeries is 11.2% at 24 months and 13.8% if all known SSSI events are included.

4. Reductions from baseline VAS pain scores were substantially less for the Cartiva group as compared to the Arthrodesis control at every time point from Week 6 to Month 24. Serious pain related adverse events were higher in the Cartiva group compared to control. See Table 55: VAS Pain Change from Baseline.

5. The FAAM Sports function scores as a change from baseline were substantially worse in the Cartiva group as compared to the Arthrodesis control at Month 6 and Month 12.

6. The FAAM ADL function scores as a change from baseline were substantially worse in the Cartiva group as compared to the Arthrodesis control at Month 6 and Month 12.

7. The FFI-R function scores as a change from baseline were substantially worse in the Cartiva group as compared to the Arthrodesis control at every time point from Week 6 to Month 24.

8. The SF-36 quality of life scores were substantially worse in the Cartiva group as compared to the Arthrodesis control group at Month 6.

9. The patient global assessment where subjects responded to the question "My overall well-being has improved since the beginning of the study?" showed lower rates of patients answering "Strongly Agree" at Month 6 (Cartiva 29% Arthrodesis 47%), Month 12 (Cartiva 33%, Arthrodesis 53%) and Month 24 (Cartiva 39%, Arthrodesis 55%).

12.3 Additional Considerations for the Benefit-Risk Assessment

As discussed in the overview above, additional considerations factor into the benefit-risk determination, and subsequently, the determination of the safety and effectiveness of a device. These considerations include uncertainty, disease characterization, patient tolerance for risk and perspective on benefit, availability of alternate treatments, risk mitigation, post-market data, and novel technology addressing unmet needs.

In this clinical study of the CARTIVA device, uncertainty was introduced by issues related to the study design including different definitions of success for each group, the method (and type) of data collected and analyzed, observations/results reported, and the absence of patient and investigator blinding. Uncertainty related to these factors was considered in the benefit-risk determination. The adequacy regarding the characterization of the medical condition under study (i.e., osteoarthritis) was also considered in the benefit-risk determination. Supplementary information, such as scientific literature on the patient population and procedure, as well as requested *post hoc* analyses of the data, was also considered.

The Panel will be asked a voting question on whether a favorable benefit-risk has been demonstrated for the PMA device for its proposed intended use.

12.4 Benefit-Risk Conclusion

The clinical study appears to demonstrate that the Cartiva subjects experienced increased maintenance range of motion while experiencing lower reductions from baseline VAS pain scores as compared to Arthrodesis at 12 and 24 months. The benefits and risks of this device have been identified. However, the study design, method of data collection and analyses, and interpretation of results, remain concerns. Based upon the benefit risk considerations, including the clinical justification of the non-inferiority

margin, primary endpoint data assessment, and adverse event profile, a determination of the relative weight of the benefits and risks of the device remains unclear.

The Panel will be asked a voting question on whether a favorable benefit-risk has been demonstrated for the PMA device for its proposed intended use.

13. POST-APPROVAL STUDY

Note: The inclusion of a Post-Approval Study section in this summary should not be interpreted to mean that FDA has reached a decision or has made a recommendation regarding the approvability of this PMA device. The presence of a post-approval study plan or commitment does not in any way alter the requirements for premarket approval and a recommendation from the Panel regarding whether the risks outweigh the benefits. The premarket data must reach the threshold for providing reasonable assurance of safety and effectiveness before the device can be found approvable and any post-approval study could be considered. The issues noted below are FDA's comments regarding potential post-approval studies, for the Panel to include in the deliberations, should FDA find the device approvable based upon the clinical premarket data.

The sponsor did not provide a post-approval study protocol in their PMA submission or in their November 20, 2015, Major Deficiency letter response. On January 20, 2016, the sponsor was requested to provide the following:

If the Cartiva Synthetic Cartilage Implant device for treatment of first metatarsophalangeal joint osteoarthritis is approved, postmarket evaluation of the longer-term safety and effectiveness of this 1st of a kind device is warranted. Due to the lack of published evidence and observational data pertaining to Cartiva SCI, a continued follow up of the clinical study cohort can be recommended as a main data source for postmarket evaluation. Based on the currently available performance data, a confirmatory risk-benefit assessment is needed with: 1) the focus on higher rates of pain/inflammatory responses in Cartiva patients vs. controls, and 2) the assessment, whether or not, there is a functional gain in mobility that would rationalize the use of Cartiva SCI vs. alternative conventional treatments.

Because no proposed Post-Approval Plan or a rationale for No Post-Approval Study was provided by the sponsor, a further epidemiological assessment with the final decision on the need for PAS and specific PAS questions will rest on the sponsor's proposal for a post-market plan. An outline is provided below that details the elements that should be included in the post-approval study protocol (if needed). More information can be found in FDA's guidance entitled "Handling Post-Approval Studies Imposed by PMA Order" located at http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm070974.htm.

- Background
- Objectives with study hypotheses
- Study design
- Study groups (including description of group)
- Patient inclusion and exclusion criteria

- Sample size calculation (based on testable hypothesis)
- Recruitment strategy (for study sites and subjects)
- Data collection: Study Endpoints
- Follow-up schedule and plan to minimize loss to follow-up.
- Statistical analysis plan
- Detailed study timeline
- Reporting requirements (interim and final reports)

The Proposed Post-Approval Plan should also include the study timeline with the following information:

- Expected date of study initiation
- Expected monthly number of study sites with IRB approvals
- Expected number of subjects enrolled per month
- Expected date of enrollment completion
- Expected date of study follow-up completion
- Expected date for Final Report submission

The Panel will be asked to comment on the need for, and elements of, a new enrollment PAS, should FDA determine that this PMA application is approvable.

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